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Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation among adults: a systematic review and network meta-analysis

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Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation among adults: a systematic review and network meta-analysis

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ABSTRACT

Introduction: Clinical trials and systematic reviews of trials involving vitamin D supplementation have mainly focused on defining the optimal amount of vitamin D dosage. However, the comparative effectiveness of different dosing schedules (i.e., daily versus bolus dosing schedule) has been largely unexplored; and currently, there is no consensus regarding the optimal vitamin D dosing schedule. Our objective is to conduct a systematic review and network meta-analysis to evaluate the comparative effectiveness and safety of steady (e.g., daily, weekly) and intermittent high-dose (e.g., monthly, yearly) vitamin D dosing schedules; and to determine the effectiveness of the various dosing schedules and combinations of treatments.

Methods and analysis: We will conduct a systematic search and review of literature from major medical databases (MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov) involving studies that compare vitamin D supplementation alone or in combination with calcium. Only randomized controlled trials (RCTs) will be considered. We will, however, consider various settings (e.g., community, institutional care) and study designs (e.g., cluster RCTs, cross-over trials). Our primary outcomes include falls and fractures including hip-fracture and non-vertebral fractures. Secondary outcomes will include muscle strength, physical performance, gait, and mobility limitation. A Bayesian network meta-analysis will be conducted, and the results will be presented in the form of treatment effect estimates and ranking probabilities, with corresponding credible intervals. Pairwise meta-analysis will also be conducted for studies reporting head-to-head comparisons. Subgroup analysis will be performed with respect to pre-determined subgroups; including vitamin D status as measured by serum 25-hydroxyvitamin D levels, age and follow up time. Sensitivity analysis will also be performed with respect to risk of bias.

Ethics and dissemination: This study is a systematic review and meta-analysis of published RCTs; therefore, no ethical approval is required. Results will be disseminated through open access peer-reviewed publications.

Systematic review registration: PROSPERO CRD112662.

Strengths and limitations of this study

- This study will provide the first systematic review and network meta-analysis involving steady dose and intermittent bolus-dose of vitamin D supplementation schedules.
- The results will provide comparative effectiveness of different vitamin D dosage schedules in relation to risk of falls and bone fractures among older adults, which is currently lacking in the literature.
- The results of this study will also provide comparative effectiveness and safety of the different supplementation schedules and dosage amounts (e.g., steady supplementation of vitamin D alone versus vitamin D plus calcium versus placebo; intermittent high-dose vitamin D alone versus vitamin D plus calcium versus placebo).
- The results of the study are dependent upon the quality of the studies included in the meta-analysis; we attempt to control for this by specifying appropriate inclusion criteria, however a number of factors are inherent issues in the RCTs themselves (e.g. compliance).
- The systematic review is limited to articles published in English language.

INTRODUCTION

The risk of falls and fractures is a major concern among the aging population as it can lead to long-term health complications (e.g., disability) and pre-mature mortality. Vitamin D is necessary for bone and muscle health [1], and vitamin D deficiency is a risk factor for falls and hip fractures among older adults [1,2]. However, the evidence for the role of vitamin D supplementation in the primary prevention of falls and fractures remains inconclusive [3–6]. To date, randomized clinical controlled trials (RCT) have administered different dosages of vitamin D supplementation with and without calcium, and the evidence for the optimal dosage of vitamin D intake is still largely unresolved [7–9]. Furthermore, the different vitamin D supplementation schedules (i.e., daily versus monthly bolus dose) used in previous trials have contributed to the conflicting evidence for the role of vitamin D supplementation in the primary prevention of falls and bone fractures [10–13]. Although, most RCTs and meta-analyses of RCTs have mainly focused on the optimal amount of vitamin D dosage, studies comparing the effectiveness of different dosage schedules have been largely unexplored.

Therapeutic drug monitoring (TDM) is a branch of clinical chemistry based on pharmacokinetics. TDM focuses on measurement of medication concentrations in the blood in order to dose appropriately to maintain drug concentration within the therapeutic window. The goal of TDM is to improve clinical outcomes by adjusting the dose of the medication to maintain target blood concentrations. A single bolus dose raises blood concentrations rapidly over minutes to hours/days before they begin to quickly decline over hours to days/weeks/months depending on the physical and chemical characteristics of the compound. On the other hand, a daily dosing schedule or an every x hour schedule with a smaller dose achieves a rise in blood concentration more gradually and is maintained by repeated dosing. The overall effectiveness of the drug is dependent upon maintaining blood concentrations within the therapeutic window. The extreme differences in vitamin D supplementation between studies, i.e., dosing amounts (e.g. 400 IU versus 300,000 IU) and schedule (e.g., daily versus one bolus dose) affects blood concentrations over time. It goes to follow that the differences in vitamin D supplementation doses and amounts would influence the clinical outcome being measured.

Currently, there is no consensus regarding the optimal vitamin D dosage schedule (i.e., frequent and steady versus intermittent high-dose) [9]. Hollis has previously suggested that steady intake of vitamin D may be more beneficial than intermittent high-dose intake because of the difference produced in serum vitamin D and 25-hydroxyvitamin D [25(OH)D] concentrations [14]. A large bolus dose results in a spike in both serum vitamin D and 25(OH)D concentrations and an immediate drop-off in serum vitamin D concentration followed by a more gradual but pronounced drop in 25(OH)D. In contrast, daily dosing schedule results in less pronounced increases and maintains serum vitamin D and 25(OH)D levels over a longer period of time [15]. Yet, numerous trials to date have administered bolus dosage schedules (e.g., bimonthly, monthly, once every 3-12 months) to increase compliance. Moreover, many published meta-analyses investigating the effects of vitamin D supplementation on skeletal health outcomes have combined daily, weekly, bi-monthly, monthly and large bolus dosage schedules together with some even including high-dose intramuscular injection [3,13]. Vitamin D dosage schedule may be an important factor to consider when assessing the totality of evidence for the beneficial role of vitamin D supplementation in relation to skeletal health outcomes.

The overall objective of this study is to conduct a systematic review and network meta-analysis (NMA) to examine comparative effectiveness and safety of frequent and steady dosage of vitamin D versus intermittent high-dose supplementation, taken alone or in combination with calcium, in reducing the risk of falls and fractures, as well as to explore differences in safety and effectiveness of the different vitamin D dosage schedules (e.g., daily, weekly, monthly, every six months, yearly).

METHODS

This protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [16] and is registered with the PROSPERO database (CRD112662, available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD 112662). Any changes to this protocol will be published in the PROSPERO registration.

Eligibility criteria:

Population

Our study population will include all adults 55 years of age and older, either residing in the community or institutional care settings.

Interventions

The following vitamin D dosage schedules will be considered for inclusion in our search and subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly, monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all studies that administer vitamin D alone (either as a supplement or as a fortified food product), or in combination with calcium.

Comparators

Eligible comparator groups within studies will include placebo or another form, dosage schedules and combination of vitamin D supplements (i.e., daily vitamin D supplementation alone or in combination with calcium will be compared to an intermittent high-dose vitamin D supplementation or in combination with calcium).

Outcomes

The primary outcomes of treatment efficacy are number of falls, overall fractures, hip fractures, non-vertebral fractures. Secondary outcomes for treatment efficacy will be muscle strength, balance, physical performance, gait, and mobility limitations. The primary outcome of treatment safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome for treatment safety.

Study designs

Only randomized controlled trials (RCT) will be included in our systematic review and evidence synthesis. We will consider all designs (e.g., cluster, cross-over, etc.) and settings (e.g., hospital, outpatient, nursing homes).

Information sources and search strategy

Major medical databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov will be searched systematically to identify all eligible studies. We will also search for additional references through hand-searching the bibliographies of included studies as well as relevant systematic reviews and meta-analyses. Search strategies include various pre-selected terms and combinations of these terms. These include terms such as vitamin D, vitamin D_3, vitamin D_2. Other terms that are used in our search relate to the primary and secondary outcomes and the combination of the outcomes with interventions. The search strategy along with all combination of terms used in our search are shown in Figure 1. All English language studies from conception to April 30, 2018 will be considered; and no restrictions are made on sample size, study period, settings and dosage of vitamin D supplementation. Only human trials involving adults 55 years or older will be included.

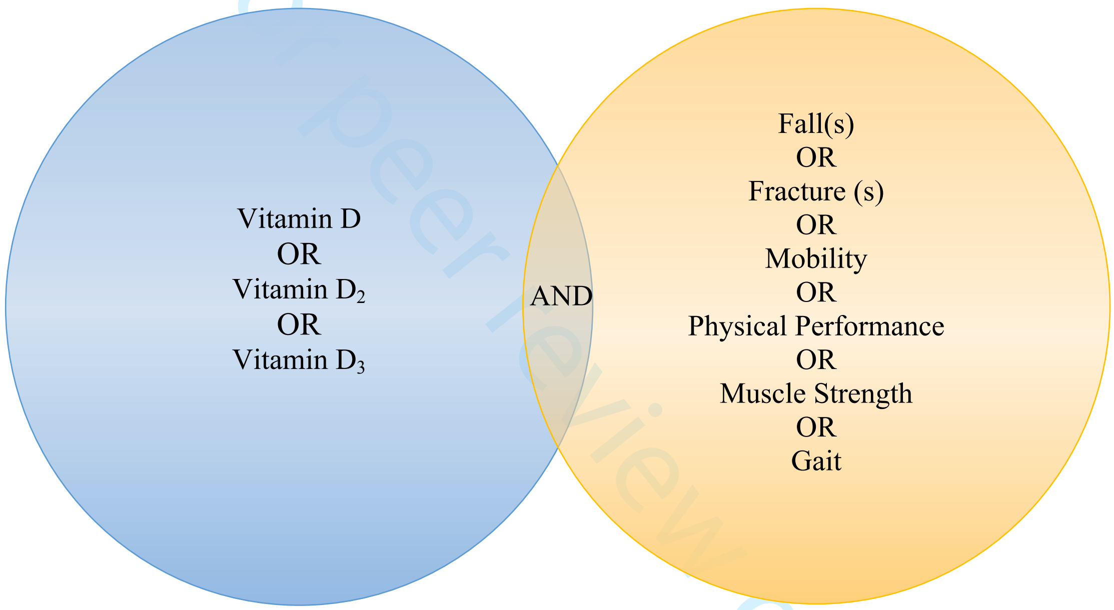

Figure 1: Search criteria for the systematic review

Data collection and analysis:

Study selection

All abstracts of relevant articles will be screened independently by two reviewers (Level I), using the pre-defined inclusion and exclusion criteria. Our inclusion criteria include RCTs administrating oral dosage of vitamin D supplementation alone or with calcium with no restrictions on the dosage amount of vitamin D or calcium. Studies will be excluded if participants are younger than 55 years of age, study design is observational in nature, and vitamin D is administered via intramuscular injection or vitamin D analogues or combined with other food/drink supplements that are fortified with other nutrients. An initial calibration exercise will be conducted prior to screening to ensure high inter-rater reliability. In these pilot runs, a random sample of 50 included abstracts will be reviewed. Inter-rater agreement will be calculated, and screening will commence when a percentage agreement of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement < 80%), the eligibility criteria will be revised, as necessary. Subsequently, each abstract will be screened by two reviewers in duplicate. A similar process will be followed for Level II screening where full texts of the studies retained from the Level I screening will be reviewed. Disagreements at both levels of screening will be resolved by discussion or consultation with a third reviewer.

Data abstraction

Study and arm level data will be extracted from all studies retained from Level II screening. A pilot assessment involving 5 studies will be conducted by the two reviewers. The data abstraction form will be reviewed and data abstracted on the 5 studies will be discussed among team members to ensure all relevant data is being extracted accurately and in a consistent manner among individuals performing data abstraction. The data abstraction form will then be modified as appropriate to ensure clarity and agreement by all team members.

Data will be abstracted on study characteristics (e.g., year of publication, authorship, location(s) of study, journal of publication, settings, latitude, follow up period, study design (e.g., cluster RCT, cross-over), total sample size as well as arm level sample size, patient characteristics (e.g., average (mean or median) age of study population, gender composition, average body mass index (or categories), living conditions (e.g., community dwelling or institution care setting), supplementation details (e.g., vitamin D dose, calcium dose, placebo, dosage schedules (e.g., daily, weekly, monthly, every 3-12 months), baseline and achieved serum 25(OH)D concentration, if measured. We will also abstract data on the primary and secondary trial-level outcomes associated with supplementation efficacy and safety (e.g., falls, injurious falls, overall fractures, hip fractures, non-vertebral fractures, muscle strength, physical performance, gait, mobility limitation, hypercalcemia, and overall mortality). Data on other relevant comorbidities and treatment related information will also be abstracted (e.g., osteoporosis, previous history of fracture, etc.). For cluster RCTs, we will also abstract additional information needed to calculate the design effect for making sample size and event level adjustments; these include cluster size, number of clusters, and intra-class correlation coefficient (ICC).

Node formation

The various forms and dosage schedules for vitamin D supplementation, as well as combinations with and without calcium will form nodes for the network meta-analysis (NMA). We anticipate an initial overall network with minimum of three connected nodes (frequent and steady vitamin D vs high-dose intermittent vitamin D vs placebo). Depending on the search results, heterogeneity across the studies, number of studies within each node as well as validity of other required assumptions for NMA (e.g., connectivity, inconsistency, transitivity), we will perform decomposition of the three nodes according, for instance, to dosage schedules (e.g., daily, weekly, monthly, etc.) and treatment combination (e.g., vitamin D alone or in combination with calcium).

Risk of bias and quality assessment

Two reviewers will independently assess the risk of bias for each included study. This will be done using the Cochrane Risk of Bias Tool [17]. Each eligible trial will be assessed for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, and selective reporting.

Outcome and effect measures

All primary and secondary outcomes are binary. As such, our outcomes are reported in the form of event frequency and sample size at an arm level. Since analysis involves Bayesian NMA, the effect size we will use is the odds ratio (OR) [18]. For studies not reporting event frequency, any effect measure reported (e.g., relative risk, risk difference) will be abstracted and converted back to event frequency or to OR.

Data synthesis

Data will be first summarized descriptively and with respect to study characteristics, outcomes measures, interventions, patient characteristics as well as other relevant variables. Interventions

291 will be carefully evaluated to clearly identify specific nodes that will be used in the NMA. If
292 feasible (i.e., if the network is connected), Bayesian random effects NMA will be conducted to
293 estimate the OR and the corresponding 95% credible intervals as well as 95% prediction
294 intervals for all comparisons, which will be reported in the form of tables and forest plots [18–
295 21]. We will also estimate treatment rankings with respect to comparative effectiveness and
296 safety; and these will be provided in the form of rank plots. Surface under the cumulative
297 ranking probabilities (SUCRA) with the corresponding 95% credible intervals (CIs) will be
298 estimated for each treatment and with respect to each of the outcomes [22]. A rank-heat plot
299 across all outcomes will also be provided [23].

300 Prior to conducting NMA, we will perform preliminary analysis to examine the various
301 assumptions required to ensure validity of NMA results. These include checking assumptions of
302 consistency and elucidating homogeneity. As such, we will first investigate global
303 inconsistencies using the design-by-treatment interaction model [24]. If inconsistency is
304 detected, we will explore local inconsistencies using the loop-specific approach [25]. Data will
305 also be examined for outliers and for potential data errors. Pair-wise estimates using Bayesian
306 meta-analysis (MA) will also be provided for all comparisons with direct (head-to-head)
307 evidence [19]. If NMA is not feasible, pairwise MA will be conducted for interventions with
308 direct evidence only and the results will be presented in the form of forest plots. We will assess
309 for the transitivity assumption to ensure that potential effect modifiers (e.g., age, BMI, care
310 settings, study duration) are balanced on average across treatment comparisons. For studies
311 involving cluster RCTs, data will be adjusted using the design effect prior to performing MA and
312 NMA.

313 Meta-regression and/or subgroup analyses will be performed to examine the effect of
314 various effect modifiers [26]. These include age, gender, baseline and achieved serum 25(OH)D
315 concentration, BMI categories, form of vitamin D (e.g., D_3 versus D_2, fortified food versus
316 supplement), co-administration with calcium, comorbidities and settings and study period. We
317 will also conduct sensitivity analysis with respect to risk of bias categories as well as other
318 source of variability revealed from our preliminary analysis to ensure consistency and
319 homogeneity. We will also perform deviance analysis to identify outliers, and sensitivity analysis
320 will be performed to ensure robustness of our results. We will use comparison adjusted funnel
321 plots to investigate presence of publication bias [27].

All NMA and MA analyses will be conducted in WinBUGS Bayesian statistical software [28]. Results will be reported as odds ratio along with the 95% CIs based on 100,000 Monte Carlo simulations and vague priors. Mode convergence will be assessed by examining the trace and history plots as well as calculating the Gelmin-Rubin statistic [29]. Forest plots and other data analyses will be performed using appropriate packages in the R statistical software [30].

ETHICS AND DISSEMINATION

This is a systematic review and meta-analysis of published trials; therefore no ethical approval is required. The risk of falls and fractures is a major concern particularly among the aging population and their caregivers [1]. Although vitamin D is necessary for bone and muscle strength, the evidence on the role of vitamin D supplementation in preventing falls and fractures remains inconclusive [2–6,13]. The different doses and dosage schedules of vitamin D supplementation used in current RCTs have largely contributed to the conflicting evidence on the effectiveness of vitamin D supplementation for the primary prevention of falls and fractures among older adults [6,8,10,12,13]. Since the dosage amount and dosing schedule of vitamin D supplementation are important factors to consider when assessing the effects of vitamin D on skeletal health outcomes, it is imperative that guidance on the optimal doses and dosage schedules for the prevention of falls and fractures are provided.

This study is the first systematic review comparing steady dose and intermittent high-dose vitamin D dosage schedules. The results will provide comparative effectiveness of these two dosage schedules in relation to risk of falls and fractures among older adults (≥ 55 years). Our results will also provide comparative effectiveness and safety of the different supplementation schedules and dosage amounts. The results from this study will facilitate evidence-informed decision making and patient care and will serve as a clinical guideline towards effective dosing schedule for vitamin D in the primary prevention of falls and fractures among older adults.

Author contributions: conception (SMK and BA), study design (SMK, BA, JSH), screening and data abstraction (BA and JEE), drafting of protocol (BA, SMK, JSH, JEE), critical review and editing of protocol (BA, SMK, JSH, JEE). All authors have read and approved the final protocol.

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BMJ Open

Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation for the prevention of falls and fractures among adults: a protocol for systematic review and network meta-analysis

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Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation for the prevention of falls and fractures among adults: a protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction: Clinical trials and systematic reviews of trials involving vitamin D supplementation have mainly focused on defining the optimal amount of vitamin D dosage. However, the comparative effectiveness of different dosing schedules (i.e., daily versus bolus dosing schedule) has been largely unexplored; and currently, there is no consensus regarding the optimal vitamin D dosing schedule. Our objective is to conduct a systematic review and network meta-analysis to evaluate the comparative effectiveness and safety of steady (e.g., daily, weekly) and intermittent high-dose (e.g., monthly, yearly) vitamin D dosing schedules; and to determine the effectiveness of the various dosing schedules and combinations of treatments.

Methods and analysis: We will conduct a systematic search and review of literature from major medical databases (MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov) involving studies that compare vitamin D supplementation alone or in combination with calcium. Only randomized controlled trials (RCTs) will be considered. We will, however, consider various settings (e.g., community, institutional care) and study designs (e.g., cluster RCTs, cross-over trials). Our primary outcomes include falls and fractures including hip-fracture and non-vertebral fractures. Secondary outcomes will include muscle strength, physical performance, gait, and mobility limitation. A Bayesian network meta-analysis will be conducted, and the results will be presented in the form of treatment effect estimates and ranking probabilities, with corresponding credible intervals. Pairwise meta-analysis will also be conducted for studies reporting head-to-head comparisons. Subgroup analysis will be performed with respect to pre-determined subgroups; including vitamin D status as measured by serum 25-hydroxyvitamin D levels, age and follow up time. Sensitivity analysis will also be performed with respect to risk of bias.

Ethics and dissemination: This study is a systematic review and meta-analysis of published RCTs; therefore, no ethical approval is required. Results will be disseminated through open access peer-reviewed publications.

Systematic review registration: PROSPERO CRD42018112662.

Strengths and limitations of this study

- This study will provide the first systematic review and network meta-analysis involving steady dose and intermittent bolus-dose of vitamin D supplementation schedules.
- The results will provide comparative effectiveness of different vitamin D dosage schedules in relation to risk of falls and bone fractures among older adults, which is currently lacking in the literature.
- The results of this study will also provide comparative effectiveness and safety of the different supplementation schedules and dosage amounts (e.g., steady supplementation of vitamin D alone versus vitamin D plus calcium versus placebo; intermittent high-dose vitamin D alone versus vitamin D plus calcium versus placebo).
- The results of the study are dependent upon the quality of the studies included in the meta-analysis; we attempt to control for this by specifying appropriate inclusion criteria, however a number of factors are inherent issues in the RCTs themselves (e.g. compliance).
- The systematic review is limited to articles published in English language.

INTRODUCTION

The risk of falls and fractures is a major concern among the aging population as it can lead to long-term health complications (e.g., disability) and pre-mature mortality. Vitamin D is necessary for bone and muscle health [1], and vitamin D deficiency is a risk factor for falls and hip fractures among older adults [1,2]. However, the evidence for the role of vitamin D supplementation in the primary prevention of falls and fractures remains inconclusive [3–6]. To date, randomized clinical controlled trials (RCT) have administered different dosages of vitamin D supplementation with and without calcium, and the evidence for the optimal dosage of vitamin D intake is still largely unresolved [7–9]. Furthermore, the different vitamin D supplementation schedules (i.e., daily versus monthly bolus dose) used in previous trials have contributed to the conflicting evidence for the role of vitamin D supplementation in the primary prevention of falls and bone fractures [10–13]. Although, most RCTs and meta-analyses of RCTs have mainly focused on the optimal amount of vitamin D dosage, studies comparing the effectiveness of different dosage schedules have been largely unexplored.

Therapeutic drug monitoring (TDM) is a branch of clinical chemistry based on pharmacokinetics. TDM focuses on measurement of medication concentrations in the blood in order to dose appropriately to maintain drug concentration within the therapeutic window. The goal of TDM is to improve clinical outcomes by adjusting the dose of the medication to maintain target blood concentrations. A single bolus dose raises blood concentrations rapidly over minutes to hours/days before they begin to quickly decline over hours to days/weeks/months depending on the physical and chemical characteristics of the compound. On the other hand, a daily dosing schedule or an every x hour schedule with a smaller dose achieves a rise in blood concentration more gradually and is maintained by repeated dosing. The overall effectiveness of the drug is dependent upon maintaining blood concentrations within the therapeutic window. Nutrient supplementation studies differ from drug trials in several ways including the fact that the drug being tested is absent in the placebo group whereas the placebo of a nutrient study will be a non-zero level (i.e., not a complete deficiency). However, dosing of a drug and supplement over time are comparable, particularly if the nutrient is water-soluble. While nutrient levels do not need to be strictly controlled for therapeutic effect, the extreme differences in vitamin D supplementation between studies, i.e., dosing amounts (e.g. 400 IU versus 300,000 IU) and schedule (e.g., daily versus one bolus dose) affects blood concentrations over time. A single high dose of vitamin D results in increased activity of 24-hydroxylase enzyme (CYP24A1) [14], and thus a bolus annual dose may result in vitamin D deficiency for a portion of the year. It goes to follow that the differences in vitamin D supplementation doses and amounts would influence the clinical outcome being measured.

Currently, there is no consensus regarding the optimal vitamin D dosage schedule (i.e., frequent and steady versus intermittent high-dose) [9]. Hollis has previously suggested that steady intake of vitamin D may be more beneficial than intermittent high-dose intake because of the difference produced in serum vitamin D and 25-hydroxyvitamin D [25(OH)D] concentrations [15]. A large bolus dose results in a spike in both serum vitamin D and 25(OH)D concentrations and an immediate drop-off in serum vitamin D concentration followed by a more gradual but pronounced drop in 25(OH)D. In contrast, daily dosing schedule results in less pronounced increases and maintains serum vitamin D and 25(OH)D levels over a longer period of time [16]. Yet, numerous trials to date have administered bolus dosage schedules (e.g., bimonthly, monthly, once every 3-12 months) to increase compliance. Moreover, many published meta-analyses investigating the effects of vitamin D supplementation on skeletal health outcomes have combined daily, weekly, bi-monthly, monthly and large bolus dosage schedules together with some even including high-dose intramuscular injection [3,13]. Vitamin D dosage schedule may be an important factor to consider when assessing the totality of evidence for the beneficial role of vitamin D supplementation in relation to skeletal health outcomes.

The overall objective of this study is to conduct a systematic review and network meta-analysis (NMA) to examine comparative effectiveness and safety of frequent and steady dosage of vitamin D versus intermittent high-dose supplementation, taken alone or in combination with calcium, in reducing the risk of falls and fractures, as well as to explore differences in safety and effectiveness of the different vitamin D dosage schedules (e.g., daily, weekly, monthly, every six months, yearly).

METHODS

This protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [17] and is registered with the PROSPERO database (CRD42018112662, available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018112662). Any changes to this protocol will be published in the PROSPERO registration.

Eligibility criteria:

Population

Our study population will include all adults who are 55 years or older or a study population with a mean or median age of 55 years or older, either residing in the community or institutional care settings.

Interventions

The following vitamin D dosage schedules will be considered for inclusion in our search and subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly, monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all studies that administer vitamin D alone (either as a supplement or as a fortified food product), or in combination with calcium. For fortified food products, we will only consider RCTs that have administered a vitamin D fortified food product and compare it to an unfortified version of the same product (e.g., fortified cheese as the intervention and unfortified cheese as the comparator) to control for any confounding effect from other nutrients when given as a fortified food product.

Comparators

Eligible comparator groups within studies will include placebo or another form, dosage schedules and combination of vitamin D supplements (i.e., daily vitamin D supplementation alone or in combination with calcium will be compared to an intermittent high-dose vitamin D supplementation or in combination with calcium).

Outcomes

The primary outcomes of treatment efficacy are number of falls, overall fractures, hip fractures, non-vertebral fractures. Secondary outcomes for treatment efficacy will be muscle strength, balance, physical performance, gait, and mobility limitations. The primary outcome of treatment safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome for treatment safety.

Study designs

Only randomized controlled trials (RCT) will be included in our systematic review and evidence synthesis. We will consider all designs (e.g., cluster, cross-over, etc.) and settings (e.g., hospital, outpatient, nursing homes). For crossover studies, due to the possibility of a carry-over effect, the Cochrane guideline and recommendations specific to crossover trial will be considered in our analysis [18]. Sensitivity analysis will also be performed to investigate the effect of such studies in the overall pooled estimates and comparative rankings.

Information sources and search strategy

Major medical databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov will be searched systematically to identify all eligible studies. We will also search for additional references through hand-searching the bibliographies of included studies as well as relevant systematic reviews and meta-analyses. Search strategies include various pre-selected terms and combinations of these terms. These include terms such as vitamin D, vitamin D_3, vitamin D_2. Other terms that are used in our search relate to the primary and secondary outcomes and the combination of the outcomes with interventions. The search strategy along with all combination of terms used in our search are shown in Table 1. All English language studies from conception to April 30, 2018 will be considered; and no restrictions are made on sample size, study period, settings and dosage of vitamin D supplementation. Only human trials involving adults who are 55 years or older or a study population with a mean or median age of 55 years or older will be included.

Table 1: Search criteria for the systematic review: EMBASE

	Database: EMBASE **Search Date:** April 30, 2018 **Time/Period:** 1974 to April 30, 2018	
Step	**Keywords** (*Including MeSH words*)	**Number of Papers**
1	Vitamin D/ or Vitamin D.mp	109,558
2	Vitamin D2.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,760
3	Vitamin D3.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14,377
4	1 or 2 or 3	116,444
5	Falls.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	54,525
6	Falls.mp. or falling/	73,654
7	5 or 6	73,654

8	4 and 7	2,703
9	fractures.mp. or fracture	211,161
10	fracture*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	357,706
11	9 or 10	357,706
12	4 and 11	15,955
13	patient mobility/ or limited mobility/ or Mobility.mp.	187,679
14	mobility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	187,679
15	13 or 14	187,679
16	4 and 15	1,046
17	endurance/ or grip strength/ or physical performance/ or muscle strength/ or Physical Performance*.mp. or fitness/	129,167
18	Physical Performance*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	20,383
19	17 or 18	129,167
20	4 and 19	1,823
21	muscle strength.mp. or muscle strength/	57,550
22	muscle strength.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	57,550
23	21 or 22	57,550
24	4 and 23	1,302
25	gait/ or gait*.mp.	79,085
26	4 and 25	641
27	mortality*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1257640)	1,257,640
28	4 and 27	7,397
29	8 or 12 or 16 or 20 or 24 or 26 or 28	24,342
	Limitations	
30	limit 29 to (english language and (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))	4,073

31	limit 29 to (english language and (meta analysis or "systematic review"))	944
32	30 or 31	4,634

Data collection and analysis:

Data management

All abstracts and full text articles will be uploaded to EndNote (version 7) software and all abstracts will be transferred to excel, where screening questions will be developed and tested for Level I and II assessments based on the inclusion and exclusion criteria.

Study selection

All abstracts of relevant articles will be screened independently by two reviewers (Level I), using the pre-defined inclusion and exclusion criteria. Our inclusion criteria include RCTs administrating oral dosage of vitamin D supplementation alone or with calcium with no restrictions on the dosage amount of vitamin D or calcium. Studies will be excluded if participants are younger than 55 years of age (mean or median age), study design is observational in nature, and vitamin D is administered via intramuscular injection or vitamin D analogues or combined with other food/drink supplements that are fortified with other nutrients. An initial calibration exercise will be conducted prior to screening to ensure high inter-rater reliability. In these pilot runs, a random sample of 50 included abstracts will be reviewed. Inter-rater agreement will be calculated, and screening will commence when a percentage agreement of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement < 80%), the eligibility criteria will be revised, as necessary. Subsequently, each abstract will be screened by two reviewers in duplicate. A similar process will be followed for Level II screening where full texts of the studies retained from the Level I screening will be reviewed. Disagreements at both levels of screening will be resolved by discussion or consultation with a third reviewer.

Data abstraction

Study and arm level data will be extracted from all studies retained from Level II screening. A pilot assessment involving 5 studies will be conducted by the two reviewers. The data abstraction form will be reviewed and data abstracted on the 5 studies will be discussed among team members to ensure all relevant data is being extracted accurately and in a consistent manner among individuals performing data abstraction. The data abstraction form will then be modified as appropriate to ensure clarity and agreement by all team members.

Data will be abstracted on study characteristics (e.g., year of publication, authorship, location(s) of study, journal of publication, settings, latitude, follow up period, study design (e.g., cluster RCT, cross-over), total sample size as well as arm level sample size, patient characteristics (e.g., average (mean or median) age of study population, gender composition, average body mass index (or categories), living conditions (e.g., community dwelling or institution care setting), supplementation details (e.g., vitamin D dose, calcium dose, placebo, dosage schedules (e.g., daily, weekly, monthly, every 3-12 months), baseline and achieved serum 25(OH)D concentration, if measured. We will also abstract data on the primary and secondary trial-level outcomes associated with supplementation efficacy and safety (e.g., falls, injurious falls, overall fractures, hip fractures, non-vertebral fractures, muscle strength, physical performance, gait, mobility limitation, hypercalcemia, and overall mortality). Data on other relevant comorbidities and treatment related information will also be abstracted (e.g., osteoporosis, previous history of fracture, etc.). For cluster RCTs, we will also abstract additional information needed to calculate the design effect for making sample size and event level adjustments; these include cluster size, number of clusters, and intra-class correlation coefficient (ICC).

Node formation

The various dosage schedules for vitamin D supplementation, as well as combinations with and without calcium will form nodes for the network meta-analysis (NMA). We anticipate an initial overall network with minimum of three connected nodes (frequent and steady vitamin D vs high-dose intermittent vitamin D vs placebo). Depending on the search results, heterogeneity across the studies, number of studies within each node as well as validity of other required assumptions for NMA (e.g., connectivity, inconsistency, transitivity), we will perform decomposition of the three nodes according, for instance, to dosage schedules (e.g., daily, weekly, monthly, etc.) and treatment combination (e.g., vitamin D alone or in combination with calcium).

Risk of bias and quality assessment

Two reviewers will independently assess the risk of bias for each included study. This will be done using the Cochrane Risk of Bias Tool [19]. Each eligible trial will be assessed for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, and selective reporting.

Outcome and effect measures

All primary and secondary outcomes are binary. As such, our outcomes are reported in the form of event frequency and sample size at an arm level. Since analysis involves Bayesian NMA, the effect size we will use is the odds ratio (OR) [20]. For studies not reporting event frequency, any effect measure reported (e.g., relative risk, risk difference) will be abstracted and converted back to event frequency or to OR.

Data synthesis

Data will be first summarized descriptively and with respect to study characteristics, outcomes measures, interventions, patient characteristics as well as other relevant variables. Interventions will be carefully evaluated to clearly identify specific nodes that will be used in the NMA. If feasible (i.e., if the network is connected), Bayesian random effects NMA will be conducted to estimate the OR and the corresponding 95% credible intervals as well as 95% prediction intervals for all comparisons, which will be reported in the form of tables and forest plots [20–23]. We will also estimate treatment rankings with respect to comparative effectiveness and safety; and these will be provided in the form of rank plots. Surface under the cumulative ranking probabilities (SUCRA) with the corresponding 95% credible intervals (CIs) will be estimated for each treatment and with respect to each of the outcomes [24]. A rank-heat plot across all outcomes will also be provided [25].

Prior to conducting NMA, we will perform preliminary analysis to examine the various assumptions required to ensure validity of NMA results. These include checking assumptions of consistency and elucidating homogeneity. As such, we will first investigate global inconsistencies using the design-by-treatment interaction model [26]. If inconsistency is detected, we will explore local inconsistencies using the loop-specific approach [27]. Data will also be examined for outliers and for potential data errors. We will also explore methodological and statistical heterogeneity as a well as heterogeneity with respect to design, population and setting differences. Statistical heterogeneity will be examined suing the I^2 statistics from all direct (head-to-head) comparisons. Careful considerations (clinical, methodological and statistical) will be done to optimally create the nodes to avoid introducing heterogeneity to the network because of node formation. If significant heterogeneity and/or inconsistency are detected, we will perform meta-regression to elucidate sources of heterogeneity as well as elucidate heterogeneity with respect to known sources of variability (e.g., population differences, risk of bias, design differences). We will also perform subgroup analysis to pool estimates from relatively homogenous groups. Sensitivity analyses will also be performed with respect to studies that are deemed to be sources of heterogeneity.

Pair-wise estimates using Bayesian meta-analysis (MA) will also be provided for all comparisons with direct (head-to-head) evidence [21]. If NMA is not feasible, pairwise MA will be conducted for interventions with direct evidence only and the results will be presented in the form of forest plots. We will assess for the transitivity assumption to ensure that potential effect modifiers (e.g., age, BMI, care settings, study duration) are balanced on average across treatment comparisons. For studies involving cluster RCTs, data will be adjusted using the design effect prior to performing MA and NMA. Meta-regression and/or subgroup analyses will be performed to examine the effect of various effect modifiers [28]. These include age, gender, baseline and achieved serum 25(OH)D concentration, BMI categories, form of vitamin D (e.g., D_3 versus D_2, fortified food versus supplement), co-administration with calcium, comorbidities and settings and study period. We will also conduct sensitivity analysis with respect to risk of bias categories as well as other source of variability revealed from our preliminary analysis to ensure consistency and homogeneity. We will also perform deviance analysis to identify outliers, and sensitivity analysis will be performed to ensure robustness of our results. We will use comparison adjusted funnel plots to investigate presence of publication bias [29].

All NMA and MA analyses will be conducted in WinBUGS Bayesian statistical software [30]. Results will be reported as odds ratio along with the 95% CIs based on 100,000 Monte Carlo simulations and vague priors. Mode convergence will be assessed by examining the trace and history plots as well as calculating the Gelmin-Rubin statistic [31]. Forest plots and other data analyses will be performed using appropriate packages in the R statistical software [32].

Patient and Public Involvement

Patients or the public will not be involved in the design or conduction of this study.

ETHICS AND DISSEMINATION

This is a systematic review and meta-analysis of published trials; therefore no ethical approval is required. The risk of falls and fractures is a major concern particularly among the aging population and their caregivers [1]. Although vitamin D is necessary for bone and muscle strength, the evidence on the role of vitamin D supplementation in preventing falls and fractures remains inconclusive [2–6,13]. The different doses and dosage schedules of vitamin D supplementation used in current RCTs have largely contributed to the conflicting evidence on the effectiveness of vitamin D supplementation for the primary prevention of falls and fractures among older adults [6,8,10,12,13]. Since the dosage amount and dosing schedule of vitamin D supplementation are important factors to consider when assessing the effects of vitamin D on skeletal health outcomes, it is imperative that guidance on the optimal doses and dosage schedules for the prevention of falls and fractures are provided.

This study is the first systematic review comparing steady dose and intermittent high-dose vitamin D dosage schedules. The results will provide comparative effectiveness of these two dosage schedules in relation to risk of falls and fractures among older adults (≥ 55 years). Our results will also provide comparative effectiveness and safety of the different supplementation schedules and dosage amounts. The results from this study will facilitate evidence-informed decision making and patient care and will serve as a clinical guideline towards effective dosing schedule for vitamin D in the primary prevention of falls and fractures among older adults.

Author contributions: conception (SMK and BA), study design (SMK, BA, JSH), screening and data abstraction (BA and JEE), drafting of protocol (BA, SMK, JSH, JEE), critical review and editing of protocol (BA, SMK, JSH, JEE). All authors have read and approved the final protocol. Guarantor of the review (SMK).

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Competing interests: None declared.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported: Yes	Information reported: No	Line number(s)
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	70
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	8-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	353-356
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	357-358
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	n/a
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	105-153
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	154-159
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	166-197
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	198-210
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1 (212-213)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	215-218
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	219-235
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	236-258
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	243-258
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	185-190; 250-253
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	270-275
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	282-293
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	294-309
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	316-324
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	310-316
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	270-275
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	294-299

Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation for the prevention of falls and fractures among adults: a protocol for systematic review and network meta-analysis

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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Research methods, Public health
Keywords:	Vitamin D, systematic review, meta-analysis, dosage schedule, Falls, bone fractures

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Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation for the prevention of falls and fractures among adults: a protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction: Clinical trials and systematic reviews of trials involving vitamin D supplementation have mainly focused on defining the optimal amount of vitamin D dosage. However, the comparative effectiveness of different dosing schedules (i.e., daily versus bolus dosing schedule) has been largely unexplored; and currently, there is no consensus regarding the optimal vitamin D dosing schedule. Our objective is to conduct a systematic review and network meta-analysis to evaluate the comparative effectiveness and safety of steady (e.g., daily, weekly) and intermittent high-dose (e.g., monthly, yearly) vitamin D dosing schedules; and to determine the effectiveness of the various dosing schedules and combinations of treatments.

Methods and analysis: We will conduct a systematic search and review of literature from major medical databases (MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov) involving studies that compare vitamin D supplementation alone or in combination with calcium. Only randomized controlled trials (RCTs) will be considered. We will, however, consider various settings (e.g., community, institutional care) and study designs (e.g., cluster RCTs, cross-over trials). Our primary outcomes include falls and fractures including hip-fracture and non-vertebral fractures. Secondary outcomes will include muscle strength, physical performance, gait, and mobility limitation. A Bayesian network meta-analysis will be conducted, and the results will be presented in the form of treatment effect estimates and ranking probabilities, with corresponding credible intervals. Pairwise meta-analysis will also be conducted for studies reporting head-to-head comparisons. Subgroup analysis will be performed with respect to pre-determined subgroups; including vitamin D status as measured by serum 25-hydroxyvitamin D levels, age and follow up time. Sensitivity analysis will also be performed with respect to risk of bias.

Ethics and dissemination: This study is a systematic review and meta-analysis of published RCTs; therefore, no ethical approval is required. Results will be disseminated through open access peer-reviewed publications.

Systematic review registration: PROSPERO CRD42018112662.

Strengths and limitations of this study

- This review will be the first of its kind to compare different vitamin D dosage schedules (steady versus intermittent bolus dosing schedule).
- The Bayesian random effect network meta-analysis will be utilized in analyzing the direct and indirect treatment effects.
- This systematic review only includes randomized controlled trials that administered oral vitamin D supplementation; the quality of included RCTs will be assessed and a sensitivity analysis will be performed to investigate the effect of study quality on the overall treatment effect.
- This systematic review is limited to articles published in English language.

INTRODUCTION

The risk of falls and fractures is a major concern among the aging population as it can lead to long-term health complications (e.g., disability) and pre-mature mortality. Vitamin D is necessary for bone and muscle health [1], and vitamin D deficiency is a risk factor for falls and hip fractures among older adults [1,2]. However, the evidence for the role of vitamin D supplementation in the primary prevention of falls and fractures remains inconclusive [3–6]. To date, randomized clinical controlled trials (RCT) have administered different dosages of vitamin D supplementation with and without calcium, and the evidence for the optimal dosage of vitamin D intake is still largely unresolved [7–9]. Furthermore, the different vitamin D supplementation schedules (i.e., daily versus monthly bolus dose) used in previous trials have contributed to the conflicting evidence for the role of vitamin D supplementation in the primary prevention of falls and bone fractures [10–13]. Although, most RCTs and meta-analyses of RCTs have mainly focused on the optimal amount of vitamin D dosage, studies comparing the effectiveness of different dosage schedules have been largely unexplored.

Currently, there is no consensus regarding the optimal vitamin D dosage schedule (i.e., frequent and steady versus intermittent high-dose) [9]. Hollis has previously suggested that steady intake of vitamin D may be more beneficial than intermittent high-dose intake because of the difference produced in serum vitamin D and 25-hydroxyvitamin D [25(OH)D] concentrations [14]. A large bolus dose results in a spike in both serum vitamin D and 25(OH)D concentrations and an immediate drop-off in serum vitamin D concentration followed by a more gradual but pronounced drop in 25(OH)D. In contrast, daily dosing schedule results in less pronounced increases and maintains serum vitamin D and 25(OH)D levels over a longer period of time [15]. Yet, numerous trials to date have administered bolus dosage schedules (e.g., bimonthly, monthly, once every 3-12 months) to increase compliance. Moreover, many published meta-analyses investigating the effects of vitamin D supplementation on skeletal health outcomes have combined daily, weekly, bi-monthly, monthly and large bolus dosage schedules together with some even including high-dose intramuscular injection [3,13]. Vitamin D dosage schedule may be an important factor to consider when assessing the totality of evidence for the beneficial role of vitamin D supplementation in relation to skeletal health outcomes.

The overall objective of this study is to conduct a systematic review and network meta-analysis (NMA) to examine comparative effectiveness and safety of frequent and steady dosage of vitamin D versus intermittent high-dose supplementation, taken alone or in combination with calcium, in reducing the risk of falls and fractures, as well as to explore differences in safety and effectiveness of the different vitamin D dosage schedules (e.g., daily, weekly, monthly, every six months, yearly).

METHODS

This protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [16] and is registered with the PROSPERO database (CRD42018112662, available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018112662). Any changes to this protocol will be published in the PROSPERO registration.

Eligibility criteria:

Population

Our study population will include all adults who are 55 years or older or a study population with a mean or median age of 55 years or older, either residing in the community or institutional care settings.

Interventions

The following vitamin D dosage schedules will be considered for inclusion in our search and subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly, monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all studies that administer vitamin D alone (either as a supplement or as a fortified food product), or in combination with calcium. For fortified food products, we will only consider RCTs that have administered a vitamin D fortified food product and compare it to an unfortified version of the same product (e.g., fortified cheese as the intervention and unfortified cheese as the comparator) to control for any confounding effect from other nutrients when given as a fortified food product.

Comparators

Eligible comparator groups within studies will include placebo or another form, dosage schedules and combination of vitamin D supplements (i.e., daily vitamin D supplementation alone or in combination with calcium will be compared to an intermittent high-dose vitamin D supplementation or in combination with calcium).

166 **Outcomes**

167 The primary outcomes of treatment efficacy are number of falls, overall fractures, hip fractures,
168 non-vertebral fractures. Secondary outcomes for treatment efficacy will be muscle strength,
169 balance, physical performance, gait, and mobility limitations. The primary outcome of treatment
170 safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome
171 for treatment safety.

172 **Study designs**

173 Only randomized controlled trials (RCT) will be included in our systematic review and evidence
174 synthesis. We will consider all designs (e.g., cluster, cross-over, etc.) and settings (e.g., hospital,
175 outpatient, nursing homes). For crossover studies, due to the possibility of a carry-over effect, the
176 Cochrane guideline and recommendations specific to crossover trial will be considered in our
177 analysis [17]. Sensitivity analysis will also be performed to investigate the effect of such studies
178 in the overall pooled estimates and comparative rankings.

179 **Information sources and search strategy**

180 Major medical databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register
181 of Controlled Trials (CENTRAL), and ClinicalTrials.gov will be searched systematically to
182 identify all eligible studies. We will also search for additional references through hand-searching
183 the bibliographies of included studies as well as relevant systematic reviews and meta-analyses.
184 Search strategies include various pre-selected terms and combinations of these terms. These
185 include terms such as vitamin D, vitamin D_3, vitamin D_2. Other terms that are used in our search
186 relate to the primary and secondary outcomes and the combination of the outcomes with
187 interventions. The search strategy along with all combination of terms used in our search are
188 shown in Table 1. All English language studies from conception to April 30, 2018 will be
189 considered; and no restrictions are made on sample size, study period, settings and dosage of
190 vitamin D supplementation. Only human trials involving adults who are 55 years or older or a
191 study population with a mean or median age of 55 years or older will be included.

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197 **Table 1: Search criteria for the systematic review: EMBASE**

	Database: EMBASE **Search Date:** April 30, 2018 **Time/Period:** 1974 to April 30, 2018	
Step	**Keywords** (*Including MeSH words*)	**Number of Papers**
1	Vitamin D/ or Vitamin D.mp	109,558
2	Vitamin D2.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,760
3	Vitamin D3.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14,377
4	1 or 2 or 3	116,444
5	Falls.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	54,525
6	Falls.mp. or falling/	73,654
7	5 or 6	73,654
8	4 and 7	2,703
9	fractures.mp. or fracture	211,161
10	fracture*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	357,706
11	9 or 10	357,706
12	4 and 11	15,955
13	patient mobility/ or limited mobility/ or Mobility.mp.	187,679
14	mobility.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	187,679
15	13 or 14	187,679
16	4 and 15	1,046
17	endurance/ or grip strength/ or physical performance/ or muscle strength/ or Physical Performance*.mp. or fitness/	129,167
18	Physical Performance*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	20,383
19	17 or 18	129,167
20	4 and 19	1,823
21	muscle strength.mp. or muscle strength/	57,550

22	muscle strength.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	57,550
23	21 or 22	57,550
24	4 and 23	1,302
25	gait/ or gait*.mp.	79,085
26	4 and 25	641
27	mortality*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1257640)	1,257,640
28	4 and 27	7,397
29	8 or 12 or 16 or 20 or 24 or 26 or 28	24,342
	Limitations	
30	limit 29 to (english language and (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))	4,073
31	limit 29 to (english language and (meta analysis or "systematic review"))	944
32	30 or 31	4,634

Data collection and analysis:

Data management

All abstracts and full text articles will be uploaded to EndNote (version 7) software and all abstracts will be transferred to excel, where screening questions will be developed and tested for Level I and II assessments based on the inclusion and exclusion criteria.

Study selection

All abstracts of relevant articles will be screened independently by two reviewers (Level I), using the pre-defined inclusion and exclusion criteria. Our inclusion criteria include RCTs administrating oral dosage of vitamin D supplementation alone or with calcium with no restrictions on the dosage amount of vitamin D or calcium. Studies will be excluded if participants are younger than 55 years of age (mean or median age), study design is observational in nature, and vitamin D is administered via intramuscular injection or vitamin D analogues or combined with other food/drink supplements that are fortified with other nutrients. An initial calibration exercise will be conducted prior to screening to ensure high inter-rater reliability. In these pilot runs, a random sample of 50 included abstracts will be reviewed. Inter-rater agreement will be calculated, and screening will commence when a percentage agreement of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement < 80%), the eligibility criteria will be revised, as necessary. Subsequently, each abstract will be screened by two reviewers in duplicate. A similar process will be followed for Level II screening where full texts of the studies retained from the Level I screening will be reviewed. Disagreements at both levels of screening will be resolved by discussion or consultation with a third reviewer.

Data abstraction

Study and arm level data will be extracted from all studies retained from Level II screening. A pilot assessment involving 5 studies will be conducted by the two reviewers. The data abstraction form will be reviewed and data abstracted on the 5 studies will be discussed among team members to ensure all relevant data is being extracted accurately and in a consistent manner among individuals performing data abstraction. The data abstraction form will then be modified as appropriate to ensure clarity and agreement by all team members.

Data will be abstracted on study characteristics (e.g., year of publication, authorship, location(s) of study, journal of publication, settings, latitude, follow up period, study design (e.g., cluster RCT, cross-over), total sample size as well as arm level sample size, patient characteristics (e.g., average (mean or median) age of study population, gender composition, average body mass index (or categories), living conditions (e.g., community dwelling or institution care setting), supplementation details (e.g., vitamin D dose, calcium dose, placebo, dosage schedules (e.g., daily, weekly, monthly, every 3-12 months), baseline and achieved serum 25(OH)D concentration, if measured. We will also abstract data on the primary and secondary trial-level outcomes associated with supplementation efficacy and safety (e.g., falls, injurious falls, overall fractures, hip fractures, non-vertebral fractures, muscle strength, physical performance, gait, mobility limitation, hypercalcemia, and overall mortality). Data on other relevant comorbidities and treatment related information will also be abstracted (e.g., osteoporosis, previous history of fracture, etc.). For cluster RCTs, we will also abstract additional information needed to calculate the design effect for making sample size and event level adjustments; these include cluster size, number of clusters, and intra-class correlation coefficient (ICC).

Node formation

The various dosage schedules for vitamin D supplementation, as well as combinations with and without calcium will form nodes for the network meta-analysis (NMA). We anticipate an initial overall network with minimum of three connected nodes (frequent and steady vitamin D vs high-dose intermittent vitamin D vs placebo). Depending on the search results, heterogeneity across the studies, number of studies within each node as well as validity of other required assumptions for NMA (e.g., connectivity, inconsistency, transitivity), we will perform decomposition of the three nodes according, for instance, to dosage schedules (e.g., daily, weekly, monthly, etc.) and treatment combination (e.g., vitamin D alone or in combination with calcium).

Risk of bias and quality assessment

Two reviewers will independently assess the risk of bias for each included study. This will be done using the Cochrane Risk of Bias Tool [18]. Each eligible trial will be assessed for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, and selective reporting.

Outcome and effect measures

All primary and secondary outcomes are binary. As such, our outcomes are reported in the form of event frequency and sample size at an arm level. Since analysis involves Bayesian NMA, the effect size we will use is the odds ratio (OR) [19]. For studies not reporting event frequency, any effect measure reported (e.g., relative risk, risk difference) will be abstracted and converted back to event frequency or to OR.

Data synthesis

Data will be first summarized descriptively and with respect to study characteristics, outcomes measures, interventions, patient characteristics as well as other relevant variables. Interventions will be carefully evaluated to clearly identify specific nodes that will be used in the NMA. If feasible (i.e., if the network is connected), Bayesian random effects NMA will be conducted to estimate the OR and the corresponding 95% credible intervals as well as 95% prediction intervals for all comparisons, which will be reported in the form of tables and forest plots [19–22]. We will also estimate treatment rankings with respect to comparative effectiveness and safety; and these will be provided in the form of rank plots. Surface under the cumulative ranking probabilities (SUCRA) with the corresponding 95% credible intervals (CIs) will be estimated for each treatment and with respect to each of the outcomes [23]. A rank-heat plot across all outcomes will also be provided [24].

Prior to conducting NMA, we will perform preliminary analysis to examine the various assumptions required to ensure validity of NMA results. These include checking assumptions of consistency and elucidating homogeneity. As such, we will first investigate global inconsistencies using the design-by-treatment interaction model [25]. If inconsistency is detected, we will explore local inconsistencies using the loop-specific approach [26]. Data will also be examined for outliers and for potential data errors. We will also explore methodological and statistical heterogeneity as a well as heterogeneity with respect to design, population and setting differences. Statistical heterogeneity will be examined using the I^2 statistics from all direct (head-to-head) comparisons. Careful considerations (clinical, methodological and statistical) will be done to optimally create the nodes to avoid introducing heterogeneity to the network because of node formation. If significant heterogeneity and/or inconsistency are detected, we will perform meta-regression to elucidate sources of heterogeneity as well as elucidate heterogeneity with respect to known sources of variability (e.g., population differences, risk of bias, design differences). We will also perform subgroup analysis to pool estimates from relatively homogenous groups. Sensitivity analyses will also be performed with respect to studies that are deemed to be sources of heterogeneity.

Pair-wise estimates using Bayesian meta-analysis (MA) will also be provided for all comparisons with direct (head-to-head) evidence [20]. If NMA is not feasible, pairwise MA will be conducted for interventions with direct evidence only and the results will be presented in the form of forest plots. We will assess for the transitivity assumption to ensure that potential effect modifiers (e.g., age, BMI, care settings, study duration) are balanced on average across treatment comparisons. For studies involving cluster RCTs, data will be adjusted using the design effect prior to performing MA and NMA. Meta-regression and/or subgroup analyses will be performed to examine the effect of various effect modifiers [27]. These include age, gender, baseline and achieved serum 25(OH)D concentration, BMI categories, form of vitamin D (e.g., D_3 versus D_2, fortified food versus supplement), co-administration with calcium, comorbidities and settings and study period. We will also conduct sensitivity analysis with respect to risk of bias categories as well as other source of variability revealed from our preliminary analysis to ensure consistency and homogeneity. We will also perform deviance analysis to identify outliers, and sensitivity analysis will be performed to ensure robustness of our results. We will use comparison adjusted funnel plots to investigate presence of publication bias [28].

All NMA and MA analyses will be conducted in WinBUGS Bayesian statistical software [29]. Results will be reported as odds ratio along with the 95% CIs based on 100,000 Monte Carlo simulations and vague priors. Mode convergence will be assessed by examining the trace and history plots as well as calculating the Gelmin-Rubin statistic [30]. Forest plots and other data analyses will be performed using appropriate packages in the R statistical software [31].

Patient and Public Involvement

Patients or the public will not be involved in the design or conduction of this study.

ETHICS AND DISSEMINATION

This is a systematic review and meta-analysis of published trials; therefore no ethical approval is required. The risk of falls and fractures is a major concern particularly among the aging population and their caregivers [1]. Although vitamin D is necessary for bone and muscle strength, the evidence on the role of vitamin D supplementation in preventing falls and fractures remains inconclusive [2–6,13]. The different doses and dosage schedules of vitamin D supplementation used in current RCTs have largely contributed to the conflicting evidence on the effectiveness of vitamin D supplementation for the primary prevention of falls and fractures among older adults [6,8,10,12,13]. Since the dosage amount and dosing schedule of vitamin D supplementation are important factors to consider when assessing the effects of vitamin D on skeletal health outcomes, it is imperative that guidance on the optimal doses and dosage schedules for the prevention of falls and fractures are provided.

This study is the first systematic review comparing steady dose and intermittent high-dose vitamin D dosage schedules. The results will provide comparative effectiveness of these two dosage schedules in relation to risk of falls and fractures among older adults (≥ 55 years). Our results will also provide comparative effectiveness and safety of the different supplementation schedules and dosage amounts. The results from this study will facilitate evidence-informed decision making and patient care and will serve as a clinical guideline towards effective dosing schedule for vitamin D in the primary prevention of falls and fractures among older adults.

Author contributions: conception (SMK and BA), study design (SMK, BA, JSH), screening and data abstraction (BA and JEE), drafting of protocol (BA, SMK, JSH, JEE), critical review and editing of protocol (BA, SMK, JSH, JEE). All authors have read and approved the final protocol. Guarantor of the review (SMK).

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Competing interests: None declared.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported: Yes	Information reported: No	Line number(s)
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	70
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	8-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	335-338
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	339-340
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	n/a
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	105-132
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	133-138
METHODS					

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	145-178
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	179-191
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1 (197-198)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	200-203
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	204-220
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	221-243
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	228-243
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	166-171; 235-238
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	253-258
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	265-276
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	277-292
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	299-307
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	293-299
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	253-258
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	277-282