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BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-027349
Article Type:	Protocol
Date Submitted by the Author:	18-Oct-2018
Complete List of Authors:	Al-khalidi, Banaz; York University, School of Kinesiology and Health Science Ewusie, Joycelyne; McMaster University, ; Hamid, Jemila; Children's Hospital of Eastern Ontario Research Institute Kimball, Samantha; Pure North S'Energy Foundation
Keywords:	Vitamin D, systematic review, meta-analysis, dosage schedule, Falls, bone fractures



Page 1 of 15

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3	1	Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation
4 5	2	among adults: a systematic review and network meta-analysis
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8	4	Banaz Al-khalidi ¹ , Joycelyne E Ewusie ² , Jemila Hamid ³ , Samantha M. Kimball ^{4,5}
9 10	5 6	
11	7	¹ School of Kinesiology and Health Science, York University, Toronto, ON, Canada
12 13	8	² Department of Health Research Methods, Evidence, and Impact, McMaster University,
14 15	9	Hamilton, ON, Canada
16 17	10	³ Children's Hospital of Eastern Ontario, Ottawa, ON, Canada
18	11	⁴ Pure North S'Energy Foundation, Calgary, AB, Canada
19 20	12	⁵ St. Mary's University, Calgary, AB, Canada
21 22	13	
23	14	Correspondence to: Samantha M. Kimball
24 25	15 16	Dura North S'Energy Foundation Cologry A.P. Canada
26	10	Pure North S'Energy Foundation, Calgary, AB, Canada
27 28	18	Tel: 403-457-5077
29	19 20	Fax: 403-457-5019
30 31	20	Fax: 403-437-3017
32	22	Tel: 403-457-5077 Fax: 403-457-5019 Email: Samantha.kimball@purenorth.ca
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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.

1 2		
- 3 4	74	Strengths and limitations of this study
5	75	• This study will provide the first systematic review and network meta-analysis involving
6 7	76	steady dose and intermittent bolus-dose of vitamin D supplementation schedules.
8 9	77	• The results will provide comparative effectiveness of different vitamin D dosage
10 11	78	schedules in relation to risk of falls and bone fractures among older adults, which is
12	79	currently lacking in the literature.
13 14	80	• The results of this study will also provide comparative effectiveness and safety of the
15 16	81	different supplementation schedules and dosage amounts (e.g., steady supplementation of
17 18	82	vitamin D alone versus vitamin D plus calcium versus placebo; intermittent high-dose
19	83	vitamin D alone versus vitamin D plus calcium versus placebo).
20 21	84	• The results of the study are dependent upon the quality of the studies included in the
22 23	85	meta-analysis; we attempt to control for this by specifying appropriate inclusion criteria,
24 25	86	however a number of factors are inherent issues in the RCTs themselves (e.g.
26	87	compliance).
27 28	88	• The systematic review is limited to articles published in English language.
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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

Page 5 of 15

BMJ Open

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.

- ⁴⁶ 161 Eligibility criteria:
- ⁴⁸ 162 **Population**

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

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2 3		
4 5 6 7	167	Interventions
	168	The following vitamin D dosage schedules will be considered for inclusion in our search and
	169	subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly,
8 9	170	monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all
10 11	171	studies that administer vitamin D alone (either as a supplement or as a fortified food product), or
12	172	in combination with calcium.
13 14	173	
15 16	174	Comparators
17	175	Eligible comparator groups within studies will include placebo or another form, dosage
18 19	176	schedules and combination of vitamin D supplements (i.e., daily vitamin D supplementation
20 21	177	alone or in combination with calcium will be compared to an intermittent high-dose vitamin D
22 23	178	supplementation or in combination with calcium).
24	179	
25 26	180	Outcomes
27 28	181	The primary outcomes of treatment efficacy are number of falls, overall fractures, hip fractures,
29	182	non-vertebral fractures. Secondary outcomes for treatment efficacy will be muscle strength,
30 31	183	balance, physical performance, gait, and mobility limitations. The primary outcome of treatment
32 33	184	safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome
34 35	185	for treatment safety.
36	186	
37 38 39 40 41 42 43	187	Study designs
	188	Only randomized controlled trials (RCT) will be included in our systematic review and evidence
	189	synthesis. We will consider all designs (e.g., cluster, cross-over, etc.) and settings (e.g., hospital,
	190	outpatient, nursing homes).
44 45	191	
46 47 48 49 50 51 52 53	192	Information sources and search strategy
	193	Major medical databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register
	194	of Controlled Trials (CENTRAL), and ClinicalTrials.gov will be searched systematically to
	195	identify all eligible studies. We will also search for additional references through hand-searching
	196	the bibliographies of included studies as well as relevant systematic reviews and meta-analyses.
54 55 56 57	197	Search strategies include various pre-selected terms and combinations of these terms. These

Page 7 of 15

198	include terms such as vitamin D, vitamin D_3 , vitamin D_2 . Other terms that are used in our search
199	relate to the primary and secondary outcomes and the combination of the outcomes with
200	interventions. The search strategy along with all combination of terms used in our search are
201	shown in Figure 1. All English language studies from conception to April 30, 2018 will be
202	considered; and no restrictions are made on sample size, study period, settings and dosage of
203	vitamin D supplementation. Only human trials involving adults 55 years or older will be
204	included.
205	
206	
207	
208	
209	Fall(s) OR
210	Fracture (s)
211	Vitamin D OR OR
212	Vitamin D ₂ AND OR
213	Vitamin D ₃ OR
214	Muscle Strength OR
215	Gait
216	
217	
218	O,
219	Figure 1: Search criteria for the systematic review
220	
221	Data collection and analysis:
222	Study selection
223	All abstracts of relevant articles will be screened independently by two reviewers (Level I), using
224	the pre-defined inclusion and exclusion criteria. Our inclusion criteria include RCTs
225	administrating oral dosage of vitamin D supplementation alone or with calcium with no
226	restrictions on the dosage amount of vitamin D or calcium. Studies will be excluded if
227	participants are younger than 55 years of age, study design is observational in nature, and
228	vitamin D is administered via intramuscular injection or vitamin D analogues or combined with
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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.

239 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

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3 4 5 6	260	adjustments; these include cluster size, number of clusters, and intra-class correlation coefficient
	261	(ICC).
7	262	
8 9	263	Node formation
10 11	264	The various forms and dosage schedules for vitamin D supplementation, as well as combinations
12	265	with and without calcium will form nodes for the network meta-analysis (NMA). We anticipate
13 14	266	an initial overall network with minimum of three connected nodes (frequent and steady vitamin
15 16	267	D vs high-dose intermittent vitamin D vs placebo). Depending on the search results,
17	268	heterogeneity across the studies, number of studies within each node as well as validity of other
18 19	269	required assumptions for NMA (e.g., connectivity, inconsistency, transitivity), we will perform
20 21 22 23	270	decomposition of the three nodes according, for instance, to dosage schedules (e.g., daily,
	271	weekly, monthly, etc.) and treatment combination (e.g., vitamin D alone or in combination with
24	272	calcium).
25 26	273	
27 28	274	Risk of bias and quality assessment
29	275	Two reviewers will independently assess the risk of bias for each included study. This will be
30 31	276	done using the Cochrane Risk of Bias Tool [17]. Each eligible trial will be assessed for the
32 33	277	following domains: random sequence generation, allocation concealment, blinding of
34 35	278	participants and personnel, blinding of outcome assessment, incomplete outcome data addressed,
36	279	and selective reporting.
37 38	280	
39 40	281	Outcome and effect measures
41 42	282	All primary and secondary outcomes are binary. As such, our outcomes are reported in the form
43	283	of event frequency and sample size at an arm level. Since analysis involves Bayesian NMA, the
44 45	284	effect size we will use is the odds ratio (OR) [18]. For studies not reporting event frequency, any
46 47	285	effect measure reported (e.g., relative risk, risk difference) will be abstracted and converted back
48	286	to event frequency or to OR.
49 50	287	
51 52	288	Data synthesis
53 54	289	Data will be first summarized descriptively and with respect to study characteristics, outcomes
54 55 56 57 58	290	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 [18-21]. 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 [22]. A rank-heat plot across all outcomes will also be provided [23].

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 [24]. If inconsistency is detected, we will explore local inconsistencies using the loop-specific approach [25]. Data will also be examined for outliers and for potential data errors. Pair-wise estimates using Bayesian meta-analysis (MA) will also be provided for all comparisons with direct (head-to-head) evidence [19]. 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 [26]. These include age, gender, baseline and achieved serum 25(OH)D concentration, BMI categories, form of vitamin D (e.g., D₃ versus D₂, 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 [27].

Page 11 of 15

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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 (\geq 55 years). Our results will also provide comparative effectiveness and safety of the different

344 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.

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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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2 3	353	Fund	ling: This research received no specific grant from any funding agency in the public,		
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Page 13 of 15

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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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-027349.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Apr-2019
Complete List of Authors:	Al-khalidi, Banaz; York University - Keele Campus, School of Kinesiology and Health Science Ewusie, Joycelyne; McMaster University, ; Hamid, Jemila; Children's Hospital of Eastern Ontario Research Institute Kimball, Samantha; Pure North S'Energy Foundation
Primary Subject Heading :	Nutrition and metabolism
Secondary Subject Heading:	Research methods
Keywords:	Vitamin D, systematic review, meta-analysis, dosage schedule, Falls, bone fractures



1	Effectiveness and safety of steady versus intermittent high dose vitamin D supplementation		
2	for the prevention of falls and fractures among adults: a protocol for systematic review and		
3	network meta-analysis		
4 5 6 7	Banaz Al-khalidi ¹ , Joycelyne E Ewusie ² , Jemila Hamid ³ , Samantha M. Kimball ^{4,5}		
8	¹ School of Kinesiology and Health Science, York University, Toronto, ON, Canada,		
9	khalidib@yorku.ca;		
0	² Department of Health Research Methods, Evidence, and Impact, McMaster University,		
1	Hamilton, ON, Canada, ewusieje@mcmaster.ca;		
2	³ Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, jehamid@cheo.on.ca;		
3	⁴ Pure North S'Energy Foundation, Calgary, AB, Canada, <u>Samantha.Kimball@purenorth.ca;</u>		
4	⁵ St. Mary's University, Calgary, AB, Canada		
5			
6 7	Correspondence to: Samantha M. Kimball		
8	Pure North S'Energy Foundation, Calgary, AB, Canada		
9 0	Tel: 403-457-5077		
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2 3	Fax: 403-457-5019		
4	Email: <u>Samantha.kimball@purenorth.ca</u>		
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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.

1 2		
3 4	73	Strengths and limitations of this study
5	74	• This study will provide the first systematic review and network meta-analysis involving
6 7	75	steady dose and intermittent bolus-dose of vitamin D supplementation schedules.
8 9	76	• The results will provide comparative effectiveness of different vitamin D dosage
10 11	77	schedules in relation to risk of falls and bone fractures among older adults, which is
12	78	currently lacking in the literature.
13 14	79	• The results of this study will also provide comparative effectiveness and safety of the
15 16	80	different supplementation schedules and dosage amounts (e.g., steady supplementation of
17 18	81	vitamin D alone versus vitamin D plus calcium versus placebo; intermittent high-dose
19	82	vitamin D alone versus vitamin D plus calcium versus placebo).
20 21	83	• The results of the study are dependent upon the quality of the studies included in the
22 23	84	meta-analysis; we attempt to control for this by specifying appropriate inclusion criteria,
24	85	however a number of factors are inherent issues in the RCTs themselves (e.g.
25 26	86	compliance).
27 28	87	• The systematic review is limited to articles published in English language.
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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

Page 5 of 19

BMJ Open

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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

166 Eligibility criteria:

167 **Population**

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168 Our study population will include all adults who are 55 years or older or a study population with 169 a mean or median age of 55 years or older, either residing in the community or institutional care 170 settings.

11 12 171 Interventions

13 172 The following vitamin D dosage schedules will be considered for inclusion in our search and 14 15 173 subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly, 16 17 174 monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all 18 175 studies that administer vitamin D alone (either as a supplement or as a fortified food product), or 19 20 176 in combination with calcium. For fortified food products, we will only consider RCTs that have 21 22 177 administered a vitamin D fortified food product and compare it to an unfortified version of the 23

24 178 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.

27 28 180 **Comparators**

Eligible comparator groups within studies will include placebo or another form, dosage
 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

 $\frac{32}{33}$ 183 alone or in combination with calcium will be compared to an intermittent high-dose vitamin D

³⁴ 184 supplementation or in combination with calcium).

36 185 Outcomes 37

186 The primary outcomes of treatment efficacy are number of falls, overall fractures, hip fractures,

 $^{39}_{40}$ 187 non-vertebral fractures. Secondary outcomes for treatment efficacy will be muscle strength,

⁴¹ 188 balance, physical performance, gait, and mobility limitations. The primary outcome of treatment

 43 189 safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome
 44 45 190 for treatment safety.

⁴⁶₄₇ 191 **Study designs**

48 192 Only randomized controlled trials (RCT) will be included in our systematic review and evidence
 49 193 synthesis. We will consider all designs (e.g., cluster, cross-over, etc.) and settings (e.g., hospital,
 51 194 outpatient, nursing homes). For crossover studies, due to the possibility of a carry-over effect, the
 53 195 Cochrane guideline and recommendations specific to crossover trial will be considered in our

Page 7 of 19

BMJ Open

1 2		
- 3 4	196	analysis [18]. Sensitivity analysis will also be performed to investigate the effect of such studies
5	197	in the overall pooled estimates and comparative rankings.
6 7	198	Information sources and search strategy
8 9 10 11 12 13 14 15 16 17 18 19 20 21	199	Major medical databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register
	200	of Controlled Trials (CENTRAL), and ClinicalTrials.gov will be searched systematically to
	201	identify all eligible studies. We will also search for additional references through hand-searching
	202	the bibliographies of included studies as well as relevant systematic reviews and meta-analyses.
	203	Search strategies include various pre-selected terms and combinations of these terms. These
	204	include terms such as vitamin D, vitamin D_3 , vitamin D_2 . Other terms that are used in our search
	205	relate to the primary and secondary outcomes and the combination of the outcomes with
	206	interventions. The search strategy along with all combination of terms used in our search are
22 23	207	shown in Table 1. All English language studies from conception to April 30, 2018 will be
24	208	considered; and no restrictions are made on sample size, study period, settings and dosage of
25 26	209	vitamin D supplementation. Only human trials involving adults who are 55 years or older or a
27 28	210	study population with a mean or median age of 55 years or older will be included.
29	211	

	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	1,760
	trade name, original title, device manufacturer, drug	
	manufacturer, device trade name, keyword, floating	
	subheading word, candidate term word]	
3	Vitamin D3.mp. [mp=title, abstract, heading word, drug	14,377
	trade name, original title, device manufacturer, drug	
	manufacturer, device trade name, keyword, floating	
	subheading word, candidate term word]	
4	1 or 2 or 3	116,444
5	Falls.mp. [mp=title, abstract, heading word, drug trade	54,525
	name, original title, device manufacturer, drug	
	manufacturer, device trade name, keyword, floating	
	subheading word, candidate term word]	
6	Falls.mp. or falling/	73,654
7	5 or 6	73,654

Table 1: Search criteria for the systematic review: EMBASE

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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

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31	limit 29 to (english language and (meta analysis or "systematic review"))	944
32	30 or 31	4,634
Data colle	ection and analysis:	7) software and all developed and tested for reviewers (Level I), using
Data mar	agement	
All abstra	cts and full text articles will be uploaded to EndNote (version	7) software and all
abstracts v	will be transferred to excel, where screening questions will be	developed and tested for
Level I an	d II assessments based on the inclusion and exclusion criteria.	
Study sel	ection	
All abstra	cts of relevant articles will be screened independently by two r	reviewers (Level I), using
the pre-de	fined inclusion and exclusion criteria. Our inclusion criteria in	clude RCTs
administra	ating oral dosage of vitamin D supplementation alone or with o	calcium with no
restriction	s on the dosage amount of vitamin D or calcium. Studies will	be excluded if
participan	ts are younger than 55 years of age (mean or median age), stud	ly design is
observatio	onal in nature, and vitamin D is administered via intramuscular	injection or vitamin D
analogues	or combined with other food/drink supplements that are fortif	ied with other nutrients.
An initial	calibration exercise will be conducted prior to screening to en-	sure high inter-rater
reliability	. In these pilot runs, a random sample of 50 included abstracts	will be reviewed. Inter-
rater agree	ement will be calculated, and screening will commence when a	a percentage agreement
of at least	80% is observed. If there is poor-moderate agreement (i.e., pe	rcentage agreement <
80%), the	eligibility criteria will be revised, as necessary. Subsequently,	each abstract will be
screened b	by two reviewers in duplicate. A similar process will be follow	ed for Level II screening
where full	texts of the studies retained from the Level I screening will be	e reviewed.
Disagreen	nents at both levels of screening will be resolved by discussion	sure high inter-rater will be reviewed. Inter- a percentage agreement rcentage agreement < each abstract will be red for Level II screening e reviewed.
third revie	ewer.	
Data abst	raction	
Study and	arm level data will be extracted from all studies retained from	Level II screening. A
pilot asses	ssment involving 5 studies will be conducted by the two review	vers. The data
	For peer review only - http://bmjopen.bmj.com/site/about/guide	lines.xhtml 9

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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).

Page 11 of 19

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	270	Risk of bias and quality assessment
	271	Two reviewers will independently assess the risk of bias for each included study. This will be
	272	done using the Cochrane Risk of Bias Tool [19]. Each eligible trial will be assessed for the
	273	following domains: random sequence generation, allocation concealment, blinding of
	274	participants and personnel, blinding of outcome assessment, incomplete outcome data addressed,
2	275	and selective reporting.
3 4	276	Outcome and effect measures
5 6	277	All primary and secondary outcomes are binary. As such, our outcomes are reported in the form
7	278	of event frequency and sample size at an arm level. Since analysis involves Bayesian NMA, the
8 9	279	effect size we will use is the odds ratio (OR) [20]. For studies not reporting event frequency, any
) 1	280	effect measure reported (e.g., relative risk, risk difference) will be abstracted and converted back
~	281	to event frequency or to OR.
4	282	Data synthesis
5	283	Data will be first summarized descriptively and with respect to study characteristics, outcomes
7 3	284	measures, interventions, patient characteristics as well as other relevant variables. Interventions
)	285	will be carefully evaluated to clearly identify specific nodes that will be used in the NMA. If
	286	feasible (i.e., if the network is connected), Bayesian random effects NMA will be conducted to
<u>-</u>	287	estimate the OR and the corresponding 95% credible intervals as well as 95% prediction
} ;	288	intervals for all comparisons, which will be reported in the form of tables and forest plots [20-
	289	23]. We will also estimate treatment rankings with respect to comparative effectiveness and
	290	safety; and these will be provided in the form of rank plots. Surface under the cumulative
	291	ranking probabilities (SUCRA) with the corresponding 95% credible intervals (CIs) will be
	292	estimated for each treatment and with respect to each of the outcomes [24]. A rank-heat plot
	293	across all outcomes will also be provided [25].
•	294	Prior to conducting NMA, we will perform preliminary analysis to examine the various
	295	assumptions required to ensure validity of NMA results. These include checking assumptions of
	296	consistency and elucidating homogeneity. As such, we will first investigate global
	297	inconsistencies using the design-by-treatment interaction model [26]. If inconsistency is
2	298	detected, we will explore local inconsistencies using the loop-specific approach [27]. Data will
•	299	also be examined for outliers and for potential data errors. We will also explore methodological
	300	and statistical heterogeneity as a well as heterogeneity with respect to design, population and

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setting differences. Statistical heterogeneity will be examined suing the I² 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., D₃ versus D₂, 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**

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

Page 13 of 19

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3 4 5 6 7 8 9	332	ETHICS AND DISSEMINATION					
	333	This is a systematic review and meta-analysis of published trials; therefore no ethical approval is					
	334	required. The risk of falls and fractures is a major concern particularly among the aging					
	335	population and their caregivers [1]. Although vitamin D is necessary for bone and muscle					
10 11	336	strength, the evidence on the role of vitamin D supplementation in preventing falls and fractures					
12	337	remains inconclusive [2-6,13]. The different doses and dosage schedules of vitamin D					
13 14	338	supplementation used in current RCTs have largely contributed to the conflicting evidence on the					
15 16 17 18 19	339	effectiveness of vitamin D supplementation for the primary prevention of falls and fractures					
	340	among older adults [6,8,10,12,13]. Since the dosage amount and dosing schedule of vitamin D					
	341	supplementation are important factors to consider when assessing the effects of vitamin D on					
20 21	342	skeletal health outcomes, it is imperative that guidance on the optimal doses and dosage					
22 23	343	schedules for the prevention of falls and fractures are provided.					
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	344	This study is the first systematic review comparing steady dose and intermittent high-					
	345	dose vitamin D dosage schedules. The results will provide comparative effectiveness of these					
	346	two dosage schedules in relation to risk of falls and fractures among older adults (\geq 55 years)					
	347	Our results will also provide comparative effectiveness and safety of the different					
	348	supplementation schedules and dosage amounts. The results from this study will facilitate					
	349	evidence-informed decision making and patient care and will serve as a clinical guideline					
	350	towards effective dosing schedule for vitamin D in the primary prevention of falls and fractures					
	351	among older adults.					
	352						
	353	Author contributions: conception (SMK and BA), study design (SMK, BA, JSH), screening					
41 42	354	and data abstraction (BA and JEE), drafting of protocol (BA, SMK, JSH, JEE), critical review					
43	355	and editing of protocol (BA, SMK, JSH, JEE). All authors have read and approved the final					
44 45	356	protocol. Guarantor of the review (SMK).					
46 47	357	Funding: This research received no specific grant from any funding agency in the public,					
48 49	358	commercial or not-for-profit sectors.					
49 50 51 52 53 54 55 56 57 58	359	Competing interests: None declared.					
	360 361 362 363						
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 PRISMA-P 2015 Checklist
 Provide Open of the protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 This checklist has been adapted for use with protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Rev and E2015 4:1

Section/topic	#	Checklist item	lr	nformation Yes	n reported No	Line number(s)
ADMINISTRATIVE IN	FORMAT					
Title						
Identification	1a	Identify the report as a protocol of a systematic review		\boxtimes		1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such $\frac{1}{2}\overline{5}$			\boxtimes	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number the Abstract		\boxtimes		70
Authors		(Q , 1)				
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide paysical mailing address of corresponding author		\boxtimes		8-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review		\boxtimes		353-356
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify such and list changes; otherwise, state plan for documenting important protocol amendments	y as		\square	n/a
Support	-					
Sources	5a	Indicate sources of financial or other support for the review		\square		357-358
Sponsor	5b	Provide name for the review funder and/or sponsor			\boxtimes	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			\boxtimes	n/a
INTRODUCTION		gies.				
Rationale	6	Describe the rationale for the review in the context of what is already known		\boxtimes		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)		\boxtimes		154-159
METHODS						
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Section/topic	#	BMJ Open by copyright, included by Copyright,	Information	n reported	Line
bection/topic	#		Yes	No	number(s)
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 be ligibility for the review			166-197
nformation sources	9	Describe all intended information sources (e.g., electronic databases, contact with study and s, trial registers, or other grey literature sources) with planned dates of coverage			198-210
earch strategy	10	Present draft of search strategy to be used for at least one electronic database, including lighted 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 ලිංකුක්			215-218
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and two independent reviewers) and two independent reviewers) are the selecting studies (e.g., two independent			219-235
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done indep the filling forms indep to the filling and confirming data from investigators	\square		236-258
oata 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	\square		243-258
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and be additional outcomes, with rationale	\square		185-190; 250- 253
Risk of bias in ndividual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whet the 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		sin N			•
	15a	Describe criteria under which study data will be quantitatively synthesized			282-293
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, netheds of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., <i>I</i> ² , Kendall's tau)			294-309
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-i grog sion)	\square		316-324
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			310-316
leta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, sele ve reporting within studies)			270-275
Confidence in umulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	\square		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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-027349.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2019
Complete List of Authors:	Al-khalidi, Banaz; York University - Keele Campus, School of Kinesiology and Health Science Ewusie, Joycelyne; McMaster University, ; Hamid, Jemila; Children's Hospital of Eastern Ontario Research Institute Kimball, Samantha; Pure North S'Energy Foundation
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



for the prevention of falls and fractures among adults: a protocol for systematic review a
network meta-analysis
Banaz Al-khalidi ¹ , Joycelyne E Ewusie ² , Jemila Hamid ³ , Samantha M. Kimball ^{4,5}
¹ School of Kinesiology and Health Science, York University, Toronto, ON, Canada,
khalidib@yorku.ca;
² Department of Health Research Methods, Evidence, and Impact, McMaster University,
Hamilton, ON, Canada, ewusieje@mcmaster.ca;
³ Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, jehamid@cheo.on.ca;
⁴ Pure North S'Energy Foundation, Calgary, AB, Canada, <u>Samantha.Kimball@purenorth.ca</u> ;
⁵ St. Mary's University, Calgary, AB, Canada
Correspondence to: Samantha M. Kimball
Pure North S'Energy Foundation, Calgary, AB, Canada
Tel: 403-457-5077
Tel: 403-457-5077 Fax: 403-457-5019 Email: Samantha.kimball@purenorth.ca
Email: <u>Samantha.kimball@purenorth.ca</u>

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.

1 2							
2 3 4	73	Strengths and limitations of this study					
5	74	• This review will be the first of its kind to compare different vitamin D dosage schedules					
6 7	75	(steady versus intermittent bolus dosing schedule).					
8 9	76	• The Bayesian random effect network meta-analysis will be utilized in analyzing the direct					
10 11	77	and indirect treatment effects.					
12	78	• This systematic review only includes randomized controlled trials that administered oral					
13 14	79	vitamin D supplementation; the quality of included RCTs will be assessed and a					
15 16	80	sensitivity analysis will be performed to investigate the effect of study quality on the					
17	81	overall treatment effect.					
18 19	82	• This systematic review is limited to articles published in English language.					
20 21	83						
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24	85	This systematic review is limited to articles published in English language.					
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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

1 2						
3 4	135	of vitamin D versus intermittent high-dose supplementation, taken alone or in combination with				
5	136	calcium, in reducing the risk of falls and fractures, as well as to explore differences in safety and				
6 7	137	effectiveness of the different vitamin D dosage schedules (e.g., daily, weekly, monthly, every six				
8 9	138	months, yearly).				
10	139	METHODS				
11 12	140	This protocol is written in accordance with the Preferred Reporting Items for Systematic Review				
13 14	141	and Meta-Analysis Protocols (PRISMA-P) [16] and is registered with the PROSPERO database				
15 16	142	(CRD42018112662, available at:				
17	143	http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018112662). Any				
18 19	144	changes to this protocol will be published in the PROSPERO registration.				
20 21	145	Eligibility criteria:				
22 23	146	Population				
24	147	Our study population will include all adults who are 55 years or older or a study population with				
25 26	148	a mean or median age of 55 years or older, either residing in the community or institutional care				
27 28	149	settings.				
29 30 31	150	Interventions				
	151	The following vitamin D dosage schedules will be considered for inclusion in our search and				
32 33	152	subsequent analyses to evaluate comparative efficacy and safety; daily, weekly, bimonthly,				
34 35	153	monthly, once every 3-12 months intake of oral vitamin D supplementation. We will consider all				
36 37 38 39 40 41 42	154	studies that administer vitamin D alone (either as a supplement or as a fortified food product), or				
	155	in combination with calcium. For fortified food products, we will only consider RCTs that have				
	156	administered a vitamin D fortified food product and compare it to an unfortified version of the				
	157	same product (e.g., fortified cheese as the intervention and unfortified cheese as the comparator)				
43	158	to control for any confounding effect from other nutrients when given as a fortified food product.				
44 45	159	Comparators				
46 47	160	Eligible comparator groups within studies will include placebo or another form, dosage				
48 49	161	schedules and combination of vitamin D supplements (i.e., daily vitamin D supplementation				
50	162	alone or in combination with calcium will be compared to an intermittent high-dose vitamin D				
51 52	163	supplementation or in combination with calcium).				
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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
- ¹⁰ 170 safety will be hypercalcemia. Overall mortality will also be considered as a secondary outcome
- 12 171 for treatment safety.

¹³ ₁₄ 172 **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 [17]. 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.

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~	Database: EMBASE Search Date: April 30, 2018 Time/Period: 1974 to April 30, 2018	
Step	Keywords (Including MeSH words)	Number of Paper
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

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22	muscle strength.mp. [mp=title, abstract, heading word,	57,550		
drug trade name, original title, device manufacturer, drug				
	manufacturer, device trade name, keyword, floating			
	subheading word, candidate term word] 22 21 or 22 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	1,257,640		
	manufacturer, device trade name, keyword, floating			
	subheading word, candidate term word] (1257640)			
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	4,073		
	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			
31	trial))	944		
51	limit 29 to (english language and (meta analysis or "systematic review"))	944		
	"systematic review"))			
32	30 or 31	4,634		
Data col	lection and analysis:			
Data ma	nagement			
All abstr	acts and full text articles will be uploaded to EndNote (version 7)	software and all		
abstracts	abstracts will be transferred to excel, where screening questions will be developed and tested for			
Level I a	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				
administ	administrating oral dosage of vitamin D supplementation alone or with calcium with no			
restrictio	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			
	nts are younger than 55 years of age (mean or median age), study	design is		

Page 9 of 18

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2211analogues or combined with other food/drink supplements that are fortified with other nutrients.212An initial calibration exercise will be conducted prior to screening to ensure high inter-rater213reliability. In these pilot runs, a random sample of 50 included abstracts will be reviewed. Inter-214rater agreement will be calculated, and screening will commence when a percentage agreement215of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement 21680%), the eligibility criteria will be revised, as necessary. Subsequently, each abstract will be217screened by two reviewers in duplicate. A similar process will be followed for Level II screening218where full texts of the studies retained from the Level I screening will be reviewed.219Disagreements at both levels of screening will be resolved by discussion or consultation with a221third reviewer.222Study and arm level data will be extracted from all studies retained from Level II screening. A223pilot assessment involving 5 studies will be conducted by the two reviewers. The data224abstraction225team members to ensure all relevant data is being extracted accurately and in a consistent manner226ang individuals performing data abstraction. The data abstraction form will then be modified227as appropriate to ensure clarity and agreement by all team members.228Data will be abstracted on study characteristics (e.g., year of publication, authorship,229location(s) of study, journal of publication, settings, latitude, follow up period, study design (e.
5212An initial calibration exercise will be conducted prior to screening to ensure high inter-rater6213reliability. In these pilot runs, a random sample of 50 included abstracts will be reviewed. Inter-7214rater agreement will be calculated, and screening will commence when a percentage agreement10215of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement <
 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
8214rater agreement will be calculated, and screening will commence when a percentage agreement11215of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement <
10215of at least 80% is observed. If there is poor-moderate agreement (i.e., percentage agreement <21680%), the eligibility criteria will be revised, as necessary. Subsequently, each abstract will be217screened by two reviewers in duplicate. A similar process will be followed for Level II screening218where full texts of the studies retained from the Level I screening will be reviewed.219Disagreements at both levels of screening will be resolved by discussion or consultation with a210third reviewer.221Data abstraction222Study and arm level data will be extracted from all studies retained from Level II screening. A223pilot assessment involving 5 studies will be conducted by the two reviewers. The data224abstraction form will be reviewed and data abstracted on the 5 studies will be discussed among225team members to ensure all relevant data is being extracted accurately and in a consistent manner226as appropriate to ensure clarity and agreement by all team members.227Data will be abstracted on study characteristics (e.g., year of publication, authorship,228location(s) of study, journal of publication, settings, latitude, follow up period, study design (e.g.,230cluster RCT, cross-over), total sample size as well as arm level sample size, patient231characteristics (e.g., average (mean or median) age of study population, gender composition,232average body mass index (or categories), living conditions (e.g., community dwelling or233institution care setting), supplementation details (e.g., vitamin D dose, calcium dose, placebo,
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43 234 dosage schedules (e.g., daily, weekly, monthly, every 3-12 months), baseline and achieved serum
$\frac{46}{47}$ 236 trial-level outcomes associated with supplementation efficacy and safety (e.g., falls, injurious
 falls, overall fractures, hip fractures, non-vertebral fractures, muscle strength, physical falls, overall fractures, hip fractures, non-vertebral fractures, muscle strength, physical
50 238 performance, gait, mobility limitation, hypercalcemia, and overall mortality). Data on other
$^{51}_{52}$ 239 relevant comorbidities and treatment related information will also be abstracted (e.g.,
$^{53}_{54}$ 240 osteoporosis, previous history of fracture, etc.). For cluster RCTs, we will also abstract additional
55 241 information needed to calculate the design effect for making sample size and event level 56
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58 59 60 For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml 9

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

Page 11 of 18

BMJ Open

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 I² 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., D₃ versus D₂, 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

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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 (\geq 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.

Page 13 of 18

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1 2		
3	335	Author contributions: conception (SMK and BA), study design (SMK, BA, JSH), screening
4 5	336	and data abstraction (BA and JEE), drafting of protocol (BA, SMK, JSH, JEE), critical review
6 7	337	and editing of protocol (BA, SMK, JSH, JEE). All authors have read and approved the final
8 9	338	protocol. Guarantor of the review (SMK).
10	339	Funding: This research received no specific grant from any funding agency in the public,
11 12	340	commercial or not-for-profit sectors.
13 14	341	Competing interests: None declared.
15 16	342 343	References:
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Page 15 of 18

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 17 of 18
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 This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table \$ in Moher D et al: Preferred reporting

 items for protocol submissions to *Systematic Reviews* from Table \$ in Moher D et al: Preferred reporting

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Rev and E2015 4:1

Section/topic	#	Checklist item		on reported	-
			Yes	No	number(s)
ADMINISTRATIVE IN	FORMAT				
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 management Abstract			70
Authors		g, , , , , , , , , , , , , , , , , , ,			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide paysical 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 a such and list changes; otherwise, state plan for documenting important protocol amendments of	as 🗌		n/a
Support		sim 2 c			
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		ies.			
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	Informatio		Line
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 criteriation of the review	Yes	No	number(s) 145-178
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study and strain 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			Table 1 (197- 198)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the to be a set of the set o			200-203
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) and get 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), on 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 or 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		Si Ž	•		
	15a	Describe criteria under which study data will be quantitatively synthesized			265-276
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, netheds of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., <i>I</i> ² , Kendall's tau)			277-292
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-i gragsion)			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, sele			253-258
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)			277-282
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