Review

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Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a 'forgotten step'

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Abstract. Annweiler C, Beauchet O (Angers University Hospital and UPRES EA 4638, University of Angers, UNAM, Angers, France; Robarts Research Institute, The University of Western Ontario, London, ON, Canada; and Biomathics, Paris, France) Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a 'forgotten step' (Review). *J Intern Med* 2015; **277**: 16–44.

Background. Previous meta-analyses to determine the efficacy of vitamin D supplementation to prevent falls in the elderly have shown mixed results. Inconsistencies might depend on the dose of supplements, suggesting that serum 25-hydroxyvitamin D (25OHD) concentration could influence the risk of falling. Our objective was to systematically review and quantitatively analyse the relationship between serum 25OHD concentration and the occurrence of falls.

Methods. A Medline search was conducted in December 2013, with no date limit, using the Medical Subject Heading terms 'Vitamin D' OR 'Ergocalciferols' OR 'Vitamin D deficiency' combined with 'Accidental Falls' OR 'Gait disorders, neurologic' OR 'Gait apraxia' OR 'Gait' OR 'Recurrent Falls' OR 'Falling'. Fixed and random-effects meta-analyses were performed to determine the following: (i) the effect size of the difference in 25OHD concentration between fallers and nonfallers and (ii) the risk of falling according to serum 25OHD concentration.

Results. Of the 659 retrieved studies, 18 observational studies – including ten cross-sectional and eight cohort studies – met the selection criteria. All were of good quality. The number of participants ranged from 80 to 2957 (44–100% women); 11.0% to 69.3% were fallers. Serum 25OHD concentrations were 0.33 × SD lower in fallers compared to nonfallers [pooled effect size 0.33; 95% confidence interval (CI) 0.18–0.47]. The risk of falls was inversely associated with serum 25OHD concentration [summary odds ratio (OR) 0.97; 95% CI 0.96–0.99]. The association between falls and hypovitaminosis D varied according to the definition used; the summary OR for falls was 1.23 (95% CI 0.94–1.60) for 25OHD <10 ng mL^{-1}, 1.44 (95% CI 1.17–1.76) for 25OHD <20 ng mL^{-1} and 0.95 (95% CI 0.81–1.11) for 25OHD <30 ng mL^{-1}.

Conclusions. Fallers have lower 25OHD concentrations, notably more often <20 ng mL^{-1}, than nonfallers. These findings help to determine the profile of target populations that would most benefit from vitamin D supplements to prevent falls.

Keywords: accidental falls, meta-analysis, older adults, vitamin D.

Introduction

In addition to its classical effects on bone metabolism, vitamin D exhibits various nonbone effects, the most of significant which is the prevention of falls with vitamin D supplementation in the elderly [1–4]. Fall prevention with vitamin D supplementation, which has been explained mainly by improvements in neuromuscular function [3, 4], is particularly important in which it may explain part of vitamin D-related prevention of nonvertebral bone fractures [5], and also because it has been studied extensively. To date, 17 randomized controlled trials (RCTs) have examined the effects of vitamin D supplementation on falls, further reinforced by nine meta-analyses of the RCTs [6]. This has led to the dissemination of information on this nonclassical effect of vitamin D within the medical and scientific community; however, so many analyses and re-analyses also eventually led to contradictory conclusions, with some analyses reporting effective prevention of falls and others reporting

inconclusive results [6]. Such diverging conclusions suggested that the efficiency of vitamin D supplementation to prevent falls in the elderly could depend on the dose of supplements, the lowest doses failing to reach serum 25-hydroxyvitamin D (25OHD) concentrations associated with a reduced fall risk (if any). This would signify that serum 25OHD concentration influences the risk of falls. It is surprising that despite the large number of publications on this topic, and whilst it would seem logical to have completed this step before conducting clinical trials, hypovitaminosis D has not yet been critically evaluated in a structured manner as a biological characteristic of fallers. This 'forgotten step' is essential to characterize target populations that would most benefit from vitamin D supplements to prevent falls. Here, our aim was to systematically review and quantitatively analyse the relationship between serum 25OHD concentrations and the occurrence of falls.

Methods

Data sources and searches

A systematic Medline literature search was conducted on 4 December 2013 with no date limit or language restriction, using the Medical Subject Heading (MeSH) terms 'Vitamin D' OR 'Ergocalciferols' OR 'Vitamin D deficiency' combined with the MeSH terms 'Accidental falls' OR 'Gait disorders, neurologic' OR 'Gait apraxia' OR 'Gait' OR the keywords 'Recurrent falls'[All Fields] OR 'Falling'[All Fields]. An iterative process was used to ensure all relevant articles had been obtained. A further hand search of the references from extracted papers was also conducted to identify potential studies not captured in the electronic database searches.

Study selection

One of the authors (CA) screened abstracts from the initial search and obtained articles deemed potentially relevant. Initial screening criteria for the abstracts were the following: (i) observation studies (case–control, cross-sectional and cohort studies were included), (ii) interventional studies, (iii) data collection of fall and serum vitamin D concentration as outcomes, and (iv) nonpregnant adult human participants. If a study met the initial selection criteria or its eligibility could not be determined from the title and abstract, the full text was retrieved. Both authors then independently assessed the full text for inclusion status. Disagreements were resolved through discussion. Papers were finally selected if serum vitamin D concentration was provided in fallers and nonfallers, or alternatively if the association between serum vitamin D status and fall was examined. The study selection is shown as a flow diagram in Fig. 1.

Of the 439 originally identified abstracts, 70 met the initial inclusion criteria (see Appendix 1). Following thorough examination, we excluded 52 of these 70 studies because falls and vitamin D were not study outcomes (n = 9 and n = 3, respectively), or because the relationship between vitamin D and falls was not examined (n = 40, including 36 interventional trials that did not provide the vitamin D status at baseline of participants with a history of falls). The remaining 18 studies were included in this review [7–24].

Data extraction and quality assessment

The quality of each study was assessed independently by both authors using the Newcastle–Ottawa Scale [25], a validated technique for assessing the quality of case–control and nonrandomized cohort studies. The instrument uses a star system to evaluate observational studies based on three criteria: participant selection, comparability of study groups and assessment of outcome or exposure (see Appendix 2). Important details regarding the methods and results of the selected articles were independently extracted and summarized by both authors (Table 1).

Definition of outcomes

We examined the serum concentration of 25OHD because this measure is generally accepted as a better indicator of vitamin D status than 1,25-dihydroxycholecalciferol [1, 2]. The study population of 'fallers' was estimated as the participants who reported at least one fall over a defined period of time. 'Nonfallers' did not report any falls during the same period of time.

Meta-analysis

All studies evaluating serum 25OHD concentrations in relation to falls were analysed. Two consecutive analyses were performed.

The first meta-analysis was to compare fallers and nonfallers. The difference in serum 25OHD

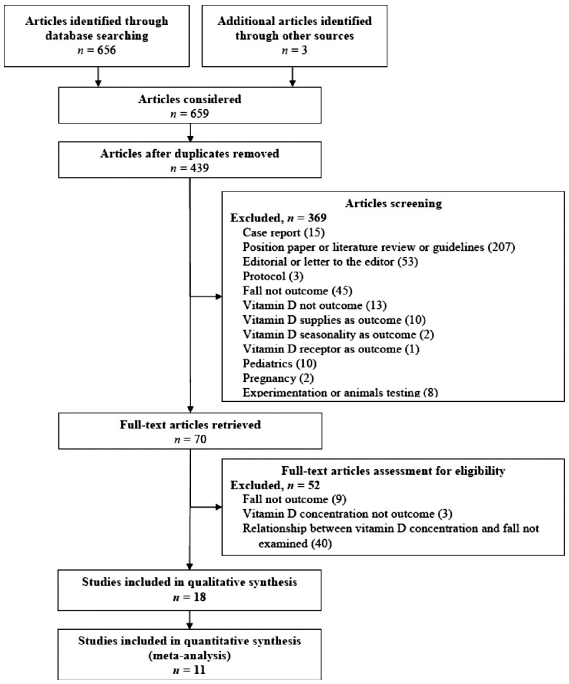

Fig. 1 *Flow diagram of selection of studies focusing on vitamin D and falls in adults.*

concentrations between the two groups was expressed in terms of a bias-corrected 'effect size' of the difference. An effect size calculator worksheet was used to derive bias-corrected effect sizes from the mean, standard deviation and size of each group (Coe's Calculator retrieved on 6 December 2013 from http://www.cemcentre.org/evidence-based-education/effect-size-calculator) (see Appendix 3). Qualitative descriptors of the effect sizes obtained were <0.3, small; 0.3–0.8, moderate; and >0.8, large [26]. Individual study data were then pooled using an inverse-variance method, and a random-effects meta-analysis was performed on the estimates with Review Manager (RevMan) version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) to generate summary values. Results were presented as forest plots (Fig. 2).

The second meta-analysis was conducted to summarize the risk of fall according to serum 25OHD concentration. When applicable, odds ratio (OR) [95% confidence interval (CI)] values were extracted from selected papers, or calculated with contingency tables and Dag-stat [27] (see Appendix 4). Statistical analyses were then performed using Computer Programs for Epidemiologists (WINPEPI) version 11.19. Results were presented as forest plots for the prediction of falls according to 25OHD concentration as a continuous variable (Fig. 3a) or as a categorical variable (Fig. 3b).

Lastly, heterogeneity between studies was assessed using Cochran's chi-squared test for homogeneity, and the amount of variation due to heterogeneity was estimated by calculating the I^2 statistic [28]. Publication bias was appraised by visual inspection of the funnel plot of effect size against the standard error (see Appendix 5).

Results

Study characteristics

The 18 studies included in this review are summarized in Table 1 [7–24]. All studies were published over the last 14 years and were judged to be of good quality using the Newcastle–Ottawa Scale (see Appendix 2). With the exception of four Australian studies [7, 10, 11, 22], they were all conducted in the Northern Hemisphere. Data collection was based either on cross-sectional (Table 1a) or prospective longitudinal design (Table 1b). No trials were identified that provided the baseline vitamin D status of participants with a history of falls. The number of participants ranged from 80 [15] to 2957 [16], with a total of 11 to 475 fallers [16, 17] and a prevalence of falls between 11% and 69% [17, 19]. The mean age of studied cohorts ranged between 63 and 86 years [9, 11, 23], and the proportion of women between 44% [21] and 100% [9, 10, 12, 13, 15, 18, 20, 24]. The serum 25OHD concentration was used as a continuous variable in six studies [7–9, 11, 18, 23] and as a categorical variable (i.e. quartiles [13] or threshold values defined *a priori* [12, 15, 16, 20]) in five studies; in the remaining seven studies, 25OHD concentration was used as both a continuous and a categorical variable [10, 14, 17, 19, 21, 22, 24]. As shown in Table 1, different methods were used to determine 25OHD concentrations, the most frequent being radioimmunoassay [9–11, 13, 15, 16, 19, 21, 23, 24]. In none of the studies was polymorphisms of the vitamin D receptor (VDR) gene evaluated. In 10 studies [10, 13, 14, 17–19, 21–24], a specific definition was used to search for fallers, and falls data were collected retrospectively and/or prospectively over a period ranging from 1 month [8] to 5 years [12]. Nonfallers received the same questionnaire and/or follow-up and reported no falls during the same period of time.

Table 1 *Summary of selected (a) cross-sectional studies and (b) longitudinal prospective studies*

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
(a)						
Stein *et al.* [7]	• Location: Melbourne, Australia (37.5°S) • *n* = 83; 66.3% female; median age 84 (IQR: 79–89) years • Institution dwellers; able to walk without assistance or supervision; no use of vitamin D and calcium supplements	• 33 fallers (i.e. ≥1 fall over undefined period of time) • 39.8% of cohort • Retrospective record • Definition of fall not provided • No difference in median age compared with nonfallers (data not provided)	• 50 nonfallers (i.e. 0 falls over undefined period of time) • Retrospective record • No difference in median age compared with fallers (data not provided)	• Modified competitive protein binding assay	• Continuous variable • Median 25OHD = 10.8 [IQR 7.2-14.8] ng mL^{-1}	Median 25OHD in • Fallers: 8.8 [IQR: • 6.9–13.2] ng mL^{-1a} • Nonfallers: 11.6 [IQR: 8–17.7] ng mL^{-1a} • $P = 0.019$ Ln 25OHD: univariate OR for falling = 0.33 [95% CI: 0.13–0.83] (not significant after adjustment for PTH)
Mowé *et al.* [8]	• Location: Oslo, Norway (59.6°N) • *n* = 309; 70.3% female; mean age 78.8 years (range: 70–91 years) • Community dwellers and inpatients; with adequate cognitive function	• 81 fallers (i.e. ≥1 fall during the last month; 79 with 25OHD assayed) • 26.2% of cohort • Retrospective record • Definition of fall not provided	• 228 fallers (i.e. 0 falls during the last month) • Retrospective record	• HPLC	• Continuous variable • Mean 25OHD = 17.8 ng mL^{-1}	Amongst community-dwellers: Mean ± SD 25OHD in • Fallers: 12.6 ± 10.0 ng mL^{-1} (n = 9) • Nonfallers: 23.0 ± 10.0 ng mL^{-1} (n = 86) • Spearman $r = -0.31$ • $P < 0.005$ Amongst patients: Mean ± SD 25OHD in • Fallers: 12.7 ± 8.8 ng mL^{-1} (n = 70) • Nonfallers: 18.0 ± 9.2 ng mL^{-1} (n = 144) • Spearman $r = -0.27$ • $P < 0.001$

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Pfeifer *et al.* [9]	• Location: Bad Pyrmont, Germany (52.0°N) • *n* = 237; 100.0% female; mean age 62.9 ± 7.4 years • Clinic for diseases of bone mineral metabolism; postmenopausal osteoporosis; no disorders affecting bone mineral metabolism	• Mean number of falls 1.5 ± 1.8 (i.e. ≥1 fall in last 5 years) • Retrospective record • Definition of fall not provided	• Retrospective record (i.e. 0 falls in last 5 years)	• RIA	• Continuous variable • Mean 25OHD = 28.0 ± 12.6 ng mL^{-1}	25OHD: Pearson *r* for number of falls = −0.122, $P < 0.01$ after adjustment for age
Holick *et al.* [12]	• Location: 61 areas in the USA (35–42°N) • *n* = 1488; 100% female; mean age 71.1 ± 9.0 years • 55 years and older; women postmenopausal for at least 2 years; with undergoing osteoporosis treatment	• 860 fallers (i.e. ≥1 fall in past 5 years) • 25.6% of cohort • 480 fallers with injury (i.e. ≥1 fall with injury in past 5 years) • 278 fallers with bone fracture (i.e. ≥1 fall with bone fracture in past 5 years) • Retrospective record with self-administered questionnaire • Definition of fall not provided	• 628 nonfallers (i.e. 0 falls in past 5 years) • Retrospective record	• TSQ Quantum Ultra triple mass-spectrometer (Thermo Finnigan Corp., San Jose, CA)	• Categorical variable (threshold: 30 ng mL^{-1}) • Mean 25OHD = 30.4 ± 13.2 ng mL^{-1}	Proportion of 25OHD <30 ng mL^{-1} in • Fallers: 51.6% • Nonfallers 52.4% • $P = 0.762$ Proportion of 25OHD <30 ng mL^{-1} in • Fallers with injury: 55.0% • Nonfallers with injury: 50.6% (*n* = 1014) • $P = 0.111$ Faller: univariate RR for 25OHD <30 ng mL^{-1} = 0.98 [95% CI:0.89–1.08] Faller with injury: RR for 25OHD <30 ng mL^{-1} = 1.08 [95% CI:0.98–1.17]

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Suzuki *et al.* [16]	• Location: Tokyo, Japan (35.7°N) • n = 2957; 67.9% female; mean age 79.7 ± 8.0 years (range 65–92) • Community dwellers; 65 years and older; without history of malignant diseases, current treatment with vitamin D, no chronic renal failure or other serious diseases affecting vitamin D regulation	• 475 fallers (i.e. ≥1 fall in past year) • 16.1% of cohort • Retrospective record • Fall defined as 'unintentional change in position resulting in coming to rest at a lower level or on the ground'	• 2482 nonfallers (i.e. 0 falls in past year) • Retrospective record	• RIA (DiaSorin, Inc., Stillwater, MN)	• Categorical variable (threshold: 20 ng mL^{-1}) • Mean 25OHD = 25.6 ng mL^{-1} (range 8–42)	Amongst males: Proportion of fallers in • 25OHD <20 ng mL^{-1} (n = 46): 6.5% (mean number of falls 2.7 ± 0.6) • 25OHD ≥20 ng mL^{-1} (n = 904): 11.1% (mean number of falls 1.8 ± 1.5) • P = 0.454 • 25OHD: multivariate OR for Faller = 1.00 [95% CI:0.95–1.06] Amongst females: Proportion of fallers in • 25OHD <20 ng mL^{-1} (n = 356): 25.8% (mean number of falls 1.7 ± 1.3) • 25OHD ≥20 ng mL^{-1} (n = 1651): 17.0% (mean number of falls 1.4 ± 1.5) • P = 0.001 25OHD: multivariate OR for Faller = 0.97 [95% CI:0.94–0.99], P = 0.010

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Shahar *et al.* [17]	• Location: Beer Sheva, Israel (31.2°N) • n = 100 (n = 54 with vitamin D assay data); 73.0% female; mean age 78.4 years (range 65–91) • Institution dwellers; 65 years and older; without serious visual impairment, inability to walk independently or impaired communication abilities; MMSE score ≥24	• 11 fallers (i.e. ≥1 fall in past year) • 11.0% of cohort • 7 recurrent fallers (i.e. ≥2 falls in past year) • Retrospective record • Fall defined as 'unexpected and involuntary loss of balance, causing the person an undesired contact with the ground' • Mean age 76.9 ± 7.2 years	• 43 nonfallers (i.e. 0 falls in past year) • Retrospective record • Mean age 79.0 ± 5.5 years	• IDS OCTEIA kit (IDS AC-57F1; Immuno-diagnostic Systems, Boldon, UK)	• Continuous and categorical variable (threshold: 10 ng mL^{-1}) • Mean 25OHD = 34.8 ng mL^{-1}	Mean ± SD 25OHD in • Fallers 31.1 ± 9.7 ng mL^{-1} • Nonfallers 35.7 ± 9.1 ng mL^{-1} • Recurrent fallers 29.0 ± 11.0 ng mL^{-1} • *F* vs. *NF:* P = 0.16 • *RF* vs. *NF:* P = 0.09 • Spearman r = −0.40, P < 0.01 for fallers Proportion of 25OHD <10 ng mL^{-1} amongst • Fallers: 10% • Nonfallers: 0%
Bernad Pineda *et al.* [20]	• Location: 63 areas in Spain (36–43°N) • n = 629; 100% female; mean age 66.6 ± 9.2 years • Community dwellers; postmenopausal women with osteoporosis consulting in rheumatology; without history of diseases affecting bone metabolism or treatment for bone metabolism disorders	• 196 fallers (i.e. ≥1 fall in past year) • 31.2% of cohort • Retrospective record • Definition of fall not provided	• 433 nonfallers (i.e. 0 falls in past year) • Retrospective record	• Information not provided	• Categorical variable (thresholds: 20 and 40 ng mL^{-1}) • Mean 25OHD = 28.6 ± 19.7 ng mL^{-1}	Distribution of fallers[a]: • 25OHD<20 ng mL^{-1}: 60% • 25OHD 20–40 ng mL^{-1}: 33% • 25OHD >40 ng mL^{-1}: 7% • P = 0.033

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Beauchet *et al.* [21]	• Location: Lyon, France (45.8°N) • *n* = 411; 44.0% female; mean age 70.4 ± 4.8 years • Community dwellers visiting health examination centre; able to understand and speak French; without acute medical illness during the past month, or history of dementia, or inability to walk 6 m unassisted	• 135 fallers (i.e. ≥1 fall in past year) • 32.8% of cohort • Retrospective record • Fall defined as 'an event resulting in a person coming to rest unintentionally on the ground or at other lower level, not as the result of a major intrinsic event or an overwhelming hazard'	• 276 nonfallers (i.e. 0 falls in past year) • Retrospective record	• RIA (DiaSorin, Inc.)	• Continuous and categorical variable (thresholds: 10 and 30 ng mL^{-1}) • Mean 25OHD = 28.6 ± 19.7 ng mL^{-1}	Mean ± SD 25OHD in • Fallers: 18.12 ± 8.43 ng mL^{-1} • Nonfallers: 19.73 ± 10.49 ng mL^{-1} • $P = 0.122$ 25OHD: univariate OR for Faller = 0.98 [95% CI:0.96–1.01], $P = 0.122$, and multivariate OR = 0.99 [95% CI:0.97–1.04], $P = 0.568$ Proportion of 25OHD <10 ng mL^{-1} in • Fallers: 17.8% • Nonfallers: 15.9% • $P = 0.638$ Proportion of 25OHD <20 ng mL^{-1} in • Fallers: 57.8% • Nonfallers: 53.6% • $P = 0.427$ Proportion of 25OHD <30 ng mL^{-1} in • Fallers: 91.9% • Nonfallers: 84.4% • $P = 0.036$

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Peterson *et al.* [23] *ISAAC study*	• Location: Portland, OR, USA (45.6°N) • *n* = 159; 74% female; mean age 85.5 years • Community dwellers; 70 years and older; not demented with an MMSE score >24; of average health for age	• 37 fallers (i.e. ≥1 fall 3 months before or 3 months after blood collection for vitamin D assay) • 23.3% of cohort • 8 recurrent fallers (i.e. ≥2 falls 3 months before or 3 months after blood collection for vitamin D assay) • Retrospective and prospective record using weekly computerized questionnaires • Fall defined as 'any fall, including a slip or trip, in which the subject came to rest on the floor, ground or on a lower level' • Mean age 86.6 years	• 122 nonfallers (i.e. 0 falls in past year and during follow-up) • Retrospective and prospective record using weekly computerized questionnaires • Mean age 85.1 years	• RIA (IDS; Immuno-diagnostic Systems Inc., Fountain Hills, AZ)	• Continuous variable • Mean 25OHD = 37.7 ng mL^{-1} (range 9–90)	Mean ± SD 25OHD in • Fallers: 32.9 ± 10.3 ng mL^{-1} • Nonfallers: 39.2 ± 15.2 ng mL^{-1} • $P < 0.01$ • Recurrent fallers 28.6 ± 11.8 ng mL^{-1} • $P = 0.04$ for RF vs. NF 25OHD: multivariate OR for Faller = 0.96 [95% CI:0.93–0.99], $P = 0.02$

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Annweiler *et al.* [24] *EPIDOS*	• Location: five areas in France: Toulouse (43.4°N), Montpellier (43.6°N), Lyon (45.5°N), Paris (48.5°N), Amiens (49.9°N) • n = 329; 100.0% female; mean age 83.2 ± 2.7 years • Community dwellers; 80 years and older	• 80 fallers (i.e. ≥1 fall in past 6 months) • 24.3% of cohort • Retrospective record • Fall defined as 'an event resulting in a person coming to rest unintentionally on the ground or at other lower level, not as the result of a major intrinsic event or an overwhelming hazard' • Mean age 83.3 ± 2.5 years	• 249 nonfallers (i.e. 0 falls in past 6 months) • Retrospective record • Mean age 83.3 ± 2.8 years	• RIA (Incstar, Stillwater, MN)	• Continuous and categorical variable (thresholds: 10 and 30 ng mL^{-1}) • Mean 25OHD = 17.7 ± 11.8 ng mL^{-1}	Proportion of 25OHD ≤10 ng mL^{-1} in • Fallers: 21.3% • Nonfallers: 24.5% • P = 0.552 Proportion of 25OHD <20 ng mL^{-1} in • Fallers: 70.0% • Nonfallers: 75.9% • P = 0.292 Proportion of 25OHD ≤30 ng mL^{-1} in • Fallers: 87.5% • Nonfallers: 91.6% • P = 0.279

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Flicker *et al.* [10]	• Location: three areas in Australia: Perth (32°S), Sydney (33.5°S), Melbourne (37.5°S) • n = 1619 • 100.0% female • Mean age 83.7 years (range 65–97) • Institution dwellers • Mean follow-up: 159 days (range 16–1033)	• 415 fallers (i.e. ≥1 fall during follow-up) • 25.6% of cohort • Prospective record using diaries completed monthly by residential care staff • Fall defined as 'an event that results in a person coming to rest inadvertently on the ground or other lower level'	• 1204 nonfallers (i.e. 0 falls during follow-up) • Prospective record	• RIA (Incstar)	• Continuous and categorical variable (thresholds: 10 and 20 ng mL^{-1}) • Mean 25OHD 14.0 ng mL^{-1}	Fall rate per person per year: • 25OHD <10 ng mL^{-1}: 1.74 • 25OHD 10–20 ng mL^{-1}: 1.59 • 25OHD >20 ng mL^{-1}: 1.39 Ln 25OHD: univariate HR for falling = 0.77 [95% CI 0.62–0.94] and multivariate HR = 0.74 [95% CI 0.59–0.94]
Sambrook *et al.* [11]	• Location: Sydney, Australia (33.5°S) • n = 637; 81.0% female; mean age 85.8 years • Institution dwellers; 65 years and older; not bed-bound; not bilateral amputees; English speakers • Mean follow-up: 10.2 months (IQR: 7.2–12)	• 274 fallers (i.e. ≥1 fall during follow-up) • 43.0% of cohort • Prospective record • Definition of fall not provided • Mean age 86.8 ± 6.5 years	• 363 nonfallers (i.e. 0 falls during follow-up) • Prospective record • Mean age 85.1 ± 6.4 years	• RIA (DiaSorin, Inc.)	• Continuous variable • Mean 25OHD 12.5 ng mL^{-1}	Mean ± SD 25OHD in Fallers: • Fallers: 11.5 ± 5.7 ng mL^{-1} • Nonfallers: 13.3 ± 6.6 ng mL^{-1} • P = 0.001 25OHD: univariate HR for falling = 0.988 [95% CI 0.980–0.996], P < 0.001 25OHD: multivariate HR for falling = 0.998 [95% CI 0.988–1.007], P = 0.06

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Faulkner *et al.* [13] *SOF study*	• Location: four areas in the USA: Baltimore, MD (39.2°N), Portland, OR (45.3°N), Minneapolis, MN (44.6°N), Pittsburgh, PA (40.3°N) • n = 389; 100.0% female; mean age 70.0 years • Community dwellers; 65 years and older, nonblack; able to walk without assistance; without bilateral hip replacement • Mean follow-up 3.8 years	• 459 falls per 1000 women (i.e. ≥1 fall during follow-up) • Prospective record by post and phone calls every 4 months • Fall defined as 'landing on the floor or ground, or falling and hitting an object like a table or a chair'	• Prospective record (i.e. 0 falls during follow-up)	• RIA	• Categorical variable (thresholds: every quartile from lowest Q1 to highest Q4) • Median 25OHD 25 (IQR: 19–31) ng mL^{-1}	Number of falls in • 25OHD Q1 (n = 105): 126 (401 women-years; 314 per 1000 women-years) • 25OHD Q2 (n = 105): 224 (409 women-years; 548 per 1000 women-years) • 25OHD Q3 (n = 81): 158 (315 women-years; 502 per 1000 women-years) • 25OHD Q4 (n = 94): 169 (367 women-years; 460 per 1000 women-years) • P = 0.055 25OHD: multivariate IRR for falling: Q1 = 1.0; Q2 = 1.58 [95% CI 1.08–2.31]; Q3 = 1.61 [95% CI 1.09–2.37]; Q4 = 1.46 [95% CI 0.99–2.15]; P-trend = 0.089

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Snijder *et al.* [14] *LASA*	• Location: three areas in the Netherlands: Amsterdam (52.2°N), Zwolle (52.5°N), Oss (51.5°N) • n = 1231; 51.1% female; mean age 75.4 years (range: 65–85) • Community and institution dwellers; 65 years and older • Follow-up 1 year	• 405 fallers (i.e. ≥1 fall during follow-up) • 32.9% of cohort • Prospective record using a fall calendar posted every 3 months • Definition of fall not provided • 142 recurrent fallers (i.e. ≥2 falls during follow-up) • Mean age 76.6 ± 6.9 years	• 826 nonfallers (i.e. 0 falls during follow-up) • Prospective record using a fall calendar • 1089 nonrecurrent fallers (i.e. 0–1 fall during follow-up) • Mean age 75.2 ± 6.4 years	• Competitive protein binding assay (Nichols Institute Diagnostics, San Juan Capistrano, CA)	• Continuous and categorical variable (thresholds: 10 and 30 ng mL^{-1}) • Mean 25OHD 21.6 ng mL^{-1}	25OHD <10 ng mL^{-1} (n=128): proportion of • Fallers 38.3% • Recurrent fallers 19.5% 25OHD ≥10 ng mL^{-1} (n = 1103): proportion of • Fallers 32.3% • Recurrent fallers 10.6% 25OHD ≤30 ng mL^{-1} (n = 1006): proportion of • Fallers 32.1% • Recurrent fallers 11.3% 25OHD >30 ng mL^{-1} (n = 225): proportion of • Fallers 36.4% • Recurrent fallers 12.4% 25OHD <10 ng mL^{-1}: univariate OR for recurrent fallers = 2.05 [95% CI 1.27–3.30], and multivariate OR = 1.78 [95% CI 1.06–2.99]

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
LeBoff *et al.* [15]	• Location: two areas in the USA: Boston, MA (42.4°N), Baltimore, MD (39.3°N) • *n* = 80; 100.0% female; mean age 79.7 ± 8.0 years • Community dwellers; with hip fractures • Follow-up 1 year	• 31 fallers (i.e. ≥1 fall during follow-up) • 38.8% of cohort • Prospective record using a diary at 1, 2, 4, 6, 9 and 12 months postfracture • Definition of fall not provided	• 49 nonfallers (i.e. 0 falls during follow-up) • Prospective record using a diary at 1, 2, 4, 6, 9 and 12 months postfracture	• RIA (DiaSorin, Inc.)	• Categorical variable (threshold: 9 ng mL^{-1}) • Mean 25OHD 30.75 ± 21.5 ng mL^{-1}	Proportion of fallers in • 25OHD ≤9 ng mL^{-1} (*n* = 30): 51.5% • 25OHD >9 ng mL^{-1} (*n* = 50): 30.0% • *P* = 0.049
Pramyothin *et al.* [18] *HOS*	• Location: Honolulu, Hawaii (21.2°N) • *n* = 495; 100.0% female; mean age 74 ± 5 years • Community dwellers; postmenopausal women of Japanese ancestry • Mean follow-up 2.7 years	• 147 fallers (i.e. ≥1 fall in past year or during follow-up) • 29.7% of cohort • 64 recurrent fallers (i.e. ≥2 falls in past year or during the follow-up) • Retrospective record + pro spective record by post and phone calls every 4 months • Fall defined as 'When you land on the floor, or other lower level (such as stairs, or a piece of furniture), by accident'	• 348 nonfallers (i.e. 0 falls in the past year or during follow-up) • Retrospective record + prospective record by post and phone calls every 4 months	• LC-MS/MS for 25OHD3 and total 25OHD	• Continuous variable • Mean 25OHD 31.94 ± 9.46 ng mL^{-1} (range 10–78)	Multivariate OR per 10 ng mL^{-1} increase in 25OHD3: • Fallers = 0.890, *P* = 0.2596 • Recurrent fallers = 0.777, *P* = 0.0804 Multivariate OR per 10 ng mL^{-1} increase in 25OHD: • Fallers: 0.913, *P* = 0.4055 • Recurrent fallers: 0.750, *P* = 0.0543

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Sai *et al.* [19]	• Location: Omaha, NE, USA (41.3°N) • *n* = 137; 65.0% female; mean age 76.7 ± 6.1 years (range 65–85) • Community dwellers; without history of central nervous system disorders including stroke/ paralysis, Parkinson's disease or Alzheimer's disease with an MMSE score <21 • Follow-up 1 year	• 95 fallers (i.e. ≥1 fall during follow-up) • 69.3% of cohort • Retrospective record using a self-reported fall questionnaire at baseline + prospective record using a falls dairy for 1 year • Fall defined as 'unintentionally coming to rest on the ground, floor or other lower level' • No difference in mean age compared with nonfallers (data not shown)	• 42 nonfallers (i.e. 0 falls in the past year and during follow-up) • Prospective record using a falls dairy for 1 year	• RIA (DiaSorin, Inc.)	• Continuous and categorical variable (thresholds: every quartile) • At the end of follow-up Mean 25OHD 24.3 ng $m^{-1}L$	Mean ± SD 25OHD in • Fallers: 23.48 ± 7.66 ng mL^{-1} • Nonfallers: 26.12 ± 7.58 ng mL^{-1} • $P = 0.084$ No significant association between 25OHD quartiles and number of falls (data not shown)

Table 1 (*Continued*)

		Participants		Vitamin D measurement		
Reference	Setting/population	Fallers	Nonfallers	Methods	Serum 25OHD measure	Results
Menant *et al.* [22] *Memory and Ageing Study*	• Location: Sydney, Australia (33.5°S) • *n* = 463; 53.4% female; mean age 78.0 ± 4.6 years (range 70–90) • Community dwellers; independent, able to walk without assistance; without dementia or other CNS disorders, or medical or psychological conditions preventing assessments • Mean follow-up 11.9 ± 0.7 months (range 6–12)	• 209 fallers (i.e. ≥1 fall during follow-up) • 45.1% of cohort • 101 recurrent fallers (i.e. ≥2 falls during follow-up) • Prospective record using monthly falls diary and follow-up telephone calls • Fall defined as 'an unexpected event in which the person comes to rest on the ground, floor or lower level' • Mean age 77.9 ± 4.8 years	• 254 nonfallers (i.e. 0 falls in past year and during follow-up) • Prospective record using monthly falls diary and follow-up telephone calls • Mean age 78.0 ± 4.5 years	• Direct competitive chemi-luminescence immunoassay kits (Liaison, DiaSorin, Germany)	• Continuous and categorical variable (thresholds: 12 and 20 ng mL^{-1}) • Mean 25OHD 24.9 ± 9.9 ng mL^{-1}	Mean ± SD 25OHD in • Fallers: 24.3 ± 9.7 ng mL^{-1} • Nonfallers: 25.3 ± 10.0 ng mL^{-1} • $P = 0.27$ Proportion of fallers not different between 25OHD <12 ng mL^{-1} and 25OHD 12–20 ng mL^{-1} (data not shown) 25OHD <20 ng mL^{-1} amongst men: IRR for fallers: 1.93 [95% CI 1.19–3.15], $P = 0.008$ 25OHD <20 ng mL^{-1} amongst women: IRR for fallers: 0.83 [95% CI 0.56–1.23], $P = 0.362$

25OHD, 25-hydroxyvitamin D; CI, confidence interval; EPIDOS, Epidemiology of Osteoporosis; HOS, Hawaii Osteoporosis Study; HPLC, high-performance liquid chromatography; HR, hazard ratio; IRR, incident rate ratio; IQR, interquartile range; ISAAC, Intelligent Systems for Assessment of Aging Changes study; LASA, Longitudinal Ageing Study Amsterdam; LC-MS/MS, liquid chromatography-tandem mass spectrometry; Ln, natural logarithm; OR, odds ratio; PTH, parathyroid hormone; RIA, radioimmunoassay; SD, standard deviation; and SOF, Study of Osteoporotic Fractures.
[a]Visually determined from figure.

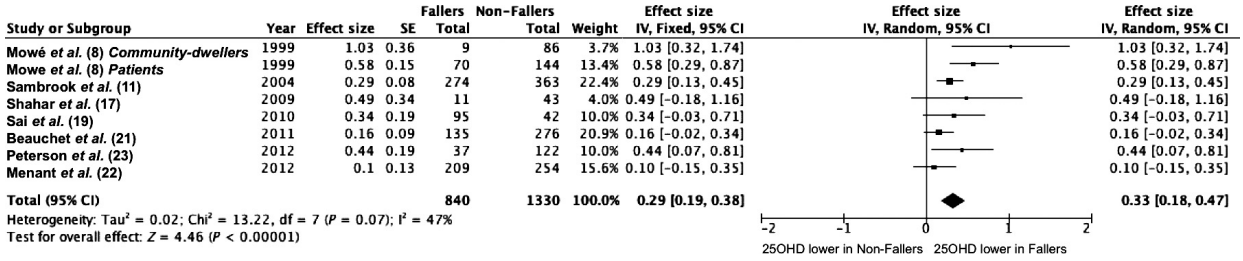

Fig. 2 *Forest plot comparing serum 25-hydroxyvitamin D concentrations in fallers and nonfallers. The area of the black box is proportional to the sample size of each study, and horizontal lines correspond to the 95% confidence interval. The black diamond represents the summary value. The vertical line corresponds to an effect size of 0.0, equivalent to no difference.*

Fallers and vitamin D

In four of the eight studies comparing serum 25OHD concentrations between the two groups, significantly lower concentrations were found in fallers compared to nonfallers (Table 1) [7, 8, 11, 23]. The proportion of fallers amongst participants with 25OHD <10, <20 and <30 ng mL^{-1} was between 38% and 53% [14, 15], 24% and 35% [16, 21], and 23% and 32% [14, 24], respectively. In one study, a decreasing trend in the prevalence of fallers was found in participants with 25OHD >40 ng mL^{-1} compared to those with 25OHD between 20 and 40 ng mL^{-1}, and compared to those with 25OHD <20 ng mL^{-1} ($P = 0.033$) [20]. Consistently, three cross-sectional analyses reported an inverse association between the serum concentration of 25OHD and the likelihood of being a faller [16, 21, 23]. There was also a positive association between hypovitaminosis D (regardless of the definition used) and being a faller [15, 16, 21]. This association remained significant after adjustment for a number of potential confounders including age, gender, body mass index, comorbidities, polypharmacy, depression, cognitive decline, muscular strength and visual acuity. A similar positive association, but of greater magnitude, was also detected between hypovitaminosis D and recurrent falling (i.e. two or more falls during the follow-up) [14], and recurrent fallers had lower 25OHD concentrations than nonfallers [23]. Finally, longitudinal prospective cohort studies showed that increased 25OHD concentrations at baseline predicted a decreased fall risk during follow-up, with hazard ratio and relative risk values <1.0 [10–12]. Similarly, in another study, the incident rate ratio (IRR) for falls increased from the highest quartile of 25OHD to the lowest quartile, with a *P*-trend value close to significance (0.089) [13]. Consistently, the IRR for falls was found to be increased approximately twofold for male participants with serum 25OHD <20 ng mL^{-1} during a mean follow-up of 12 months [22].

Results of meta-analyses

For ease of interpretation, results of published studies were included in two meta-analyses. The first meta-analysis evaluated the differences in serum 25OHD concentrations between 840 fallers and 1330 nonfallers in seven studies (Fig. 2) [8, 11, 17, 19, 21–23]. One study (reporting lower serum 25OHD concentration in fallers compared to nonfallers) could not be included in the meta-analysis because the median and interquartile range of serum 25OHD concentration, but not the mean ± standard deviation, were reported [7]. All effect sizes were positive, ranging from 0.10 to 1.03 (see Appendix 3), on a scale where 0 corresponded to no difference between fallers and nonfallers, and positive effect sizes indicated that fallers have lower 25OHD concentrations than nonfallers. In four reports, the lower limits of the CIs for the effect size were greater than zero [8, 11, 23]. The total random effect size of 0.33 (95% CI 0.18–0.47) indicated that the average serum 25OHD concentration amongst fallers was 0.33 × the SD below the average concentration of nonfallers (Fig. 2). This represents a 'moderate' association between low 25OHD concentration and falls [26], which is 'educationally significant' according to Wolf (i.e. 'something is learnt') [29]. Using the 'Common Language Effect Size' approach of McGraw and Wong, the probability is about 33% that a faller would have a lower serum 25OHD concentration than a nonfaller if both individuals were chosen at random from a population [30].

A second meta-analysis was conducted to examine falls in relation to serum 25OHD concentration.

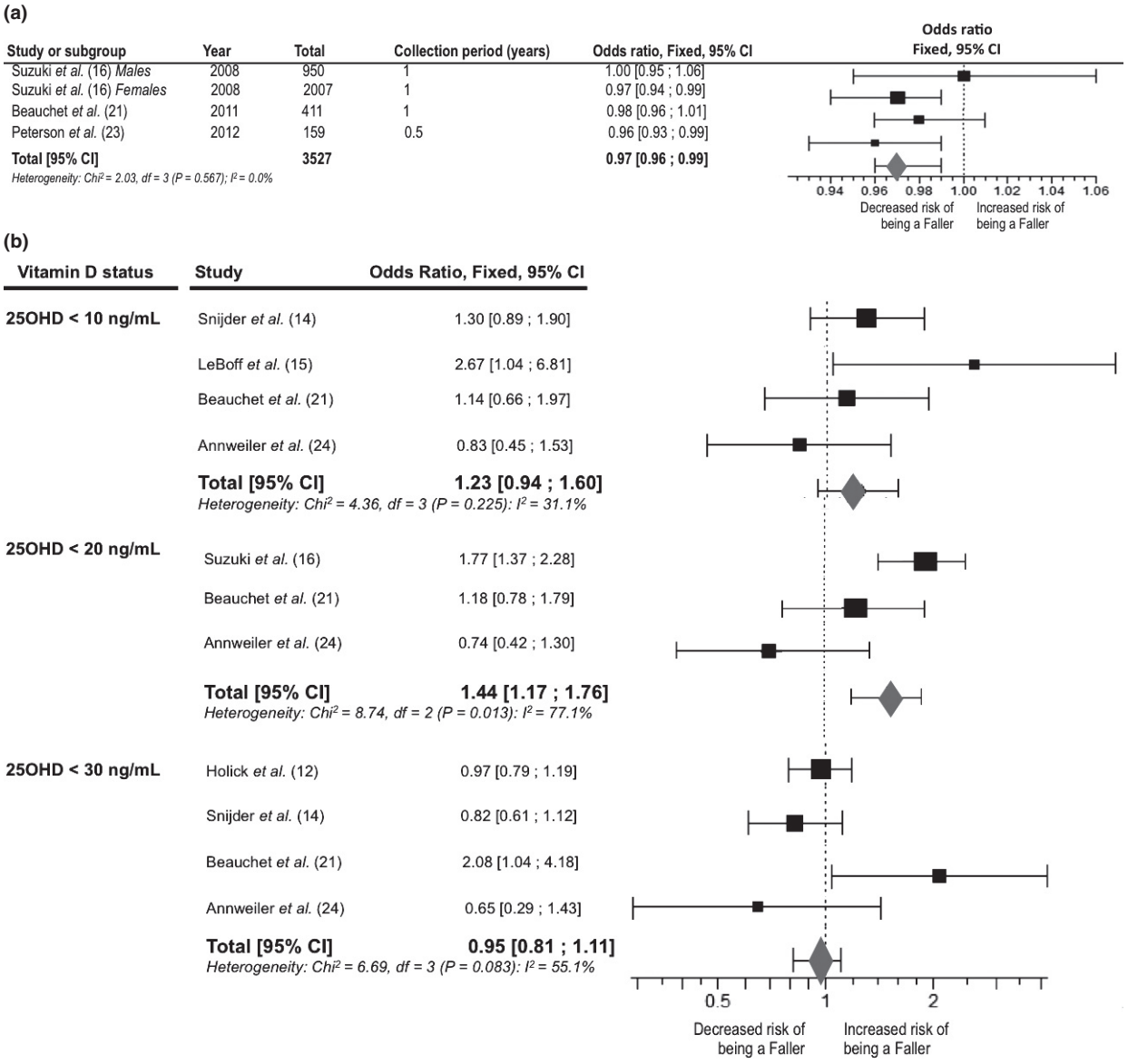

Fig. 3 *Forest plots showing the risk of being a faller according to serum 25-hydroxyvitamin D concentration as a continuous variable (a) and hypovitaminosis D (b). The area of the black box is proportional to the sample size of each study, and horizontal lines correspond to the 95% confidence interval. The grey diamonds represent the summary value. The dashed lines correspond to an odds ratio of 1.0, equivalent to no association.*

Whilst using serum 25OHD concentration as a continuous variable, the summary OR for falls was 0.97 (95% CI 0.96–0.99; $Q = 2.03$, df = 3, $P = 0.567$; $I^2 = 0.0\%$) (Fig. 3a) [16, 21, 23]. Additionally, using thresholds relevant for clinicians, the summary OR for falls was 1.23 (95% CI 0.94–1.60) for 25OHD <10 ng mL^{-1}, 1.44 (95% CI 1.17–1.76) for <20 ng mL^{-1} and 0.95 (95% CI 0.81–1.11) for <30 ng mL^{-1} (Fig. 3b).

Discussion

This systematic review and meta-analysis provides evidence that serum 25OHD concentrations are

lower in fallers compared to nonfallers and highlights a direct cross-sectional and longitudinal association between lower 25OHD concentrations and falls, specifically with concentrations <20 ng mL^{-1}.

Vitamin D and falls

Our results indicated a 'moderate' association between lower 25OHD concentration and falls, with 25OHD concentrations being 0.33 SD lower in fallers compared to nonfallers (Fig. 2). How vitamin D and falls are associated can be explained in two ways. First, falls may precipitate lower 25OHD concentrations. The adverse outcomes of falls include trauma, hospitalization, loss of independence and institutionalization, which in turn may result in insufficient exposure to the sun to synthesize adequate amounts of vitamin D, as well as feeding difficulties with subsequent inadequate consumption of vitamin D-rich foods [1, 2]. Such restrictions of exogenous sources of vitamin D could then lead to low vitamin D serum concentrations amongst fallers. However, this first hypothesis is weakened by the fact that, in the selected longitudinal prospective studies, vitamin D status at baseline predicted the occurrence of incident falls [10, 11, 13–15]. In addition, supplementation trials showed that correcting hypovitaminosis D prevented falls [3, 4, 6], thereby highlighting a second possible scenario in which lower serum 25OHD concentrations increase the risk of falls.

Avoiding falls requires correct neuromuscular function to maintain posture and balance during motor activities. This explains why, although there are multitudes of recognized fall risk factors, abnormalities in muscle and central nervous system (CNS) function predict a particularly high fall risk. Several lines of evidence suggest the existence of a link between vitamin D and muscles. Cases of myopathy have been described in individuals with profound vitamin D deficiency, associated with proximal lower limb muscle weakness [31]. Muscle biopsies showed predominantly type II muscle fibre atrophy, i.e. the fast-twitch fibres recruited to prevent falls [32]. The relationship between vitamin D and muscular strength remains controversial as a larger number of clinical trials showing a lack of effect of vitamin D supplementation on muscle strength have been reported compared to studies showing beneficial effects [33]. A recent meta-analysis showed no improvement in muscle strength after vitamin D supplementation [34]. It thus appears that vitamin D might affect neuromuscular function and fall risk in a way that not only involves the muscle but also involves the CNS [35].

Growing evidence supports the notion that vitamin D is involved in brain function [36–38]; it regulates the gene expression of several neurotrophins [39] and regulates intraneuronal calcium homoeostasis and oxidative and inflammatory changes in the brain [38, 40], thus promoting neuron viability and function. Specifically, VDRs are present in almost all brain areas including structures involved in motor control and balance such as the substantia nigra, hypothalamus and cerebellum [41]. The influence of vitamin D on motor control and on the pathophysiology of falls was recently confirmed with magnetic resonance spectroscopy, as reduced neuronal function was reported in the caudal primary motor cortex of elderly individuals with hypovitaminosis D [42].

It should be noted that not all elderly individuals will fall, even though most have a reduced vitamin D concentration. It is thus unlikely that low vitamin D concentration by itself explains the occurrence of every fall. This is probably why we found a U-shaped association between hypovitaminosis D and falls, with the 25OHD threshold of 20 ng mL^{-1} being associated with falls (although this was not the case for the other two previously proposed thresholds, i.e. 10 and 30 ng mL^{-1}) (Fig. 3b). However, the reason for this finding remains unclear. The explanation we propose is that the fall risk amongst participants with either very low or particularly high 25OHD concentrations is not only related to vitamin D but also related to other specific risk factors. Below 10 ng mL^{-1}, it can be assumed that participants are older with poorer health and a number of advanced diseases increasing the risk of falling independently of vitamin D status [43]. Conversely, above 30 ng mL^{-1}, participants are likely to be elderly individuals in good physical health with a high degree of mobility and, thus, an increased probability of falling. The involvement of the risk-taking that results from higher vitamin D levels has already been emphasized in an Australian clinical trial that showed, amongst older adults who received a massive dose of vitamin D supplements, a renewed walk with consequent greater risk-taking and more falls [44]. Moreover, it is also possible that participants with high vitamin D status formerly had 25OHD levels <10 ng mL^{-1} and received vitamin D supplements, for example to treat osteoporosis. The same reasoning has already been used to explain the

U-shaped relation between vitamin D status and frailty in women, which was absent in men [45, 46]. Finally, a high 25OHD concentration of approximately 30 ng mL^{-1} may have masked the differential impact (if such impact exists) of vitamin D on falls between cases and controls because it was probably higher than the physiological neuromuscular requirements. The exact magnitude of these requirements remains unknown. Of note, a previous meta-analysis of RCTs demonstrated that a serum 25OHD concentration of 24 ng mL^{-1} was necessary to prevent falls [3]. Consistently, physiological serum 25OHD concentrations are at least 20 ng mL^{-1} amongst healthy individuals intensively exposed to sunlight in tropical regions [2]. In line with the definitions of hypovitaminosis D proposed by the World Health Organization (WHO) [47] and the Institute of Medicine [48], we propose this threshold as a reasonable target for the elderly with regard to falls.

Critical literature analysis

Differences in populations and methodology may partly explain some inconsistencies in the individual previously published studies.

First, in all cases, no information about the number of participants required to show a cross-sectional association or to predict hypovitaminosis D-related falls was reported, and studies did not include a power analysis. As a consequence, equivocal or negative results could be the result of small sample sizes with a lack of statistical power.

Secondly, some divergent results could also be related to the definition of 'fallers', which varied between studies. According to the WHO, a fall is 'an event which results in a person coming to rest inadvertently on the ground or floor or other lower level' [49]. Of the 18 studies selected in our review, only 10 have clearly defined the term fall [10, 13, 16–19, 21–24], including eight using a definition similar to that of the WHO [10, 16, 18, 19, 21–24]. Furthermore, the collection period was different from one study to another, ranging from 1 month to 5 years for the retrospective collection [8, 9, 12], and from 159 days to 3.8 years for the prospective collection [10, 13]. Thus, even using an equivalent definition of fall, being a faller in the study by Holick *et al.* [12] (i.e. having fallen at least once in the last 5 years) should not be interpreted in the same way as being a faller in the study by Mowé *et al.* [8] (i.e. having fallen at least once in the last month). Moreover, the retrospective collection of falling data in several studies may have underestimated the frequency of falls. This is usually underreported because of the cognitive decline of those who fail to remember falling and because reporting depends on the occurrence of fall-related adverse health outcomes [50]. A systematic review showed that the recall bias could also be related to the methods used to report falls [51]. Prospective registration systems, shorter recall periods or the use of fall diaries have proven superior to other methods of data collection and could lead to a substantial increase in the number of reported falls.

Thirdly, as highlighted above, inconsistencies may result from differences in the choice of 25OHD threshold used to define hypovitaminosis D. We found that serum 25OHD concentrations lower than 20 ng mL^{-1} were associated with falling (Fig. 3b). As a consequence, categorizing populations with either too low or too high threshold concentrations may have reduced the association (if any) between vitamin D and falling. This finding is also consistent with results from supplementation studies as most inconclusive trials, in which it was found that vitamin D supplementation did not prevent falling, recruited participants with serum 25OHD either below 10 ng mL^{-1} [52–55] or as a high as 30 ng mL^{-1} [56–58], and thus, their risk of falling might have been at least in part independent of vitamin D status. Finally, this is also in line with research into nonbone effects of vitamin D, because the greatest risk of cancer, infections and cardiovascular and metabolic diseases appears to be associated with 25OHD concentrations below 20 ng mL^{-1} [59].

Fourthly, another explanation for inconclusive results may be related to polymorphisms of the *VDR* gene as recent evidence suggests that these polymorphisms may confer genetic risk for falls. Individuals with some variants appear to be less sensitive to vitamin D and more likely to develop muscle weakness or to experience cognitive decline. For instance, higher quadriceps isometric and concentric strength was found in f/f homozygotes compared to F allele carriers [60]. Similarly, a significant association has been shown between the *VDR* gene *APA1* polymorphism and the occurrence of Alzheimer's disease [61]: the *Aa* genotype increases the risk of Alzheimer's disease 2.3-fold compared to the *AA* genotype. Taken together,

these findings suggest that polymorphisms in the ligand-binding site of the *VDR* gene affect vitamin D-related neuromuscular effects and increase the risk of falls. Unfortunately, none of the selected studies took into account *VDR* polymorphisms, although it could obviously shed new light on inconclusive and negative results.

Finally, it is worth noting that the methods of serum collection and duration of preservation before 25OHD assay were not reported by the authors of any of the selected studies. The effects of temperature, light and collection vial as well as the effects of long-term serum storage on measurements are uncertain, especially regarding 25OHD stability.

Study limitations

Some potential limitations of this review should be considered. In particular, whilst a meta-analysis of effect sizes is equivalent to a meta-analysis of odds ratios – albeit with loss of power – when there is an underlying normal distribution and common variance [62], this assumption may be not entirely correct in some populations selected in the present analysis because of relatively small sample sizes. Furthermore, the summary effect size we found should be interpreted with caution as the qualitative and quantitative analyses indicated substantial heterogeneity (Fig. 2). However, the use of a random-effects meta-analysis model controlled for this limitation and compensated for the different distributions of effect across the different studies [63]. Finally, inspection of the funnel plot suggests the presence of publication bias; i.e. an empty quadrant in which potentially small unpublished studies may have shown a smaller effect size (see Appendix 5). However, the funnel plot was broadly within the pseudo 95% confidence limits, which makes publication bias less likely.

Implications for practice and research

The existing body of evidence suggests that (i) fallers have lower serum vitamin D concentrations than nonfallers and (ii) decreased 25OHD concentration, especially <20 ng mL^{-1}, is associated with increased fall risk. The implications for practice and research are manifold. First, our results support the idea that age-related hypovitaminosis D is a risk factor for falls and may explain part of the tendency of the elderly to fall. Secondly, these findings reinforce the notion of hypovitaminosis D as a biological characteristic of elderly fallers, which supports the proposal that older adults with a history of falls should routinely receive vitamin D supplementation to prevent both bone and non-bone adverse events. Thirdly, these results provide a strong rationale for conducting clinical trials in elderly fallers as these participants are likely to have low vitamin D levels at baseline, which is expected to reveal the negative effect on falling of vitamin D supplements [64, 65]. In particular, future clinical trials should recruit elderly fallers with an initial concentration of serum 25OHD between 10 and 20 ng mL^{-1}.

From the clinical perspective, our findings help to further elucidate the profile of the ideal target populations, which is the first step towards providing effective guidelines on the proper use of vitamin D supplements for fall prevention in the elderly.

Conclusions

Amongst the elderly, fallers have lower serum 25OHD concentrations, notably more often <20 ng mL^{-1}, than nonfallers. The association with falling for 25OHD <10 ng mL^{-1} or <30 ng mL^{-1} did not reach statistical significance. These findings provide a rationale for prescribing vitamin D supplementation amongst elderly fallers and help to determine the profile of the subpopulations that would most benefit from vitamin D supplements to prevent falls.

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Conflict of interest statement

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Authors' contributions

CA had full access to all of the study data and was responsible for study concept and design, acquisition, analysis and interpretation of data, the

conduct of the research, drafting of the manuscript, administrative, technical or material support and study supervision. In addition, CA has the right to publish any and all data, separate and apart from the attitudes of the sponsor. OB was responsible for acquisition and interpretation of data and critical revision of the manuscript for important intellectual content. Both authors reviewed the manuscript prior to submission.

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Appendix: 1

Publications meeting the initial inclusion criteria

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Fall not outcome

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Appendix: 2

Quality assessment of included studies using the Newcastle-Ottawa scale

	Selection				Comparability		Exposure/outcome			
Reference	Fallers definition adequate	Representativeness of Fallers	Selection of Nonfallers	Definition of Nonfallers	Age and sex	Additional factors	Ascertainment of exposure	Same method for Fallers and Nonfallers	Nonresponse rate	Score
Stein *et al.* [7]		*	*		*	*	*	*		6
Mowé *et al.* [8]		*	*		*	*	*	*		6
Pfeifer *et al.* [9]		*	*		*		*	*		6
Flicker *et al.* [10]	*	*	*			*	*	*	*	7
Sambrook *et al.* [11]		*	*		*	*	*	*	*	7
Holick *et al.* [12]		*	*		*	*	*	*		6
Faulkner *et al.* [13]	*	*	*	*		*	*	*	*	8
Snijder *et al.* [14]	*	*	*	*	*	*	*	*	*	9
LeBoff *et al.* [15]		*	*		*	*	*	*		6
Suzuki *et al.* [16]		*	*		*	*	*	*		6
Shahar *et al.* [17]	*	*	*		*	*	*	*	*	8
Pramyothin *et al.* [18]	*	*	*	*	*	*	*	*	*	9
Sai *et al.* [19]	*	*	*	*	*	*	*	*	*	9
Bernad Pineda *et al.* [20]		*	*		*		*	*		5
Beauchet *et al.* [21]	*	*	*		*	*	*	*		7
Menant *et al.* [22]	*	*	*		*		*	*		6
Peterson *et al.* [23]	*	*	*		*		*	*		6
Annweiler *et al.* [24]	*	*	*		*	*	*	*		7

Note High-quality choices are identified with an asterisk. The more asterisks allocated to a study, the better quality it was. A study could be awarded a maximum of one asterisk for each numbered item within the 'Selection' and 'Exposure/Outcome' categories. A maximum of two asterisks could be given for the 'Comparability' category.

Appendix: 3

Serum 25-hydroxyvitamin D concentrations in studies comparing fallers and nonfallers with effect size estimates for the difference

	Fallers			Nonfallers			Effect Size			
Reference	*n*	Mean	Standard deviation	*n*	Mean	Standard deviation	Uncorrected	Bias corrected *	Standard error	95% CI
Mowé *et al.* [8] community-dwellers	9	12.6	10.0	86	23.0	10.0	1.03	1.04	0.36	0.32; 1.74
Mowé *et al.* [8] patients	70	12.7	8.8	144	18.0	9.2	0.58	0.58	0.15	0.29; 0.87
Sambrook *et al.* [11]	274	11.5	5.7	363	13.3	6.6	0.29	0.29	0.08	0.13; 0.45
Shahar *et al.* [17]	11	31.1	9.7	43	35.7	9.1	0.49	0.50	0.34	−0.18; 1.16
Sai *et al.* [19]	95	23.5	7.7	42	26.1	7.6	0.34	0.34	0.19	−0.03; 0.71
Beauchet *et al.* [21]	135	18.1	8.4	276	19.7	10.5	0.16	0.16	0.11	−0.02; 0.34
Menant *et al.* [22]	209	24.3	9.7	254	25.3	10.0	0.10	0.10	0.09	−0.15; 0.35
Peterson *et al.* [23]	37	32.9	10.3	122	39.2	15.2	0.44	0.44	0.19	0.07; 0.81

Note CI, confidence interval.
* Hedges' correction.

Appendix: 4

Prevalence of hypovitaminosis D (hypoD) in studies comparing fallers and nonfallers with odds ratio estimates

	Total	Faller		Nonfaller		Odds ratio for faller		
Reference	*n*	*n*	*n* (%) with hypoD	*n*	*n* (%) with hypoD	Estimate	Standard error	95% CI
HypoD defined as 25OHD <10 ng mL^{-1}								
Snijder *et al.* [14]	1231	405	49 (12.1)	826	79 (9.6)	1.30	1.21	0.89; 1.90
LeBoff *et al.* [15]	80	31	16 (51.6)	49	14 (23.7)	2.67	1.61	1.04; 6.81
Beauchet *et al.* [21]	411	135	24 (17.8)	276	44 (15.9)	1.14	1.32	0.66; 1.97
Annweiler *et al.* [24]	329	80	17 (21.3)	249	61 (24.6)	0.83	1.36	0.45; 1.53
HypoD defined as 25OHD <20 ng mL^{-1}								
Suzuki *et al.* [16]	2957	475	95 (20.0)	2482	307 (12.37)	1.77	1.14	1.37; 2.28
Beauchet *et al.* [21]	411	135	78 (57.8)	276	148 (53.6)	1.18	1.24	0.78; 1.79
Annweiler *et al.* [24]	329	80	56 (70.0)	249	188 (75.8)	0.74	1.33	0.42; 1.30

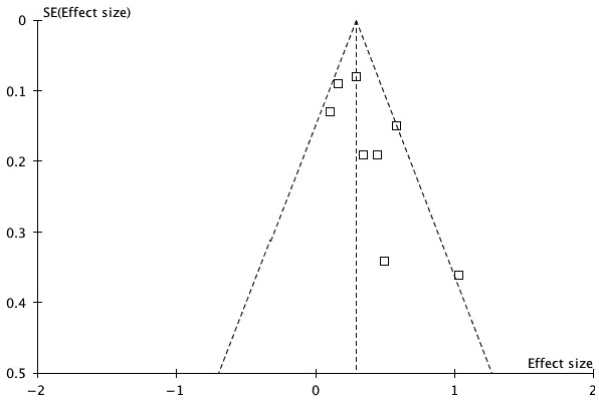
Appendix: 4 (*Continued*)

Reference	Total *n*	Faller *n*	Faller *n* (%) with hypoD	Nonfaller *n*	Nonfaller *n* (%) with hypoD	Odds ratio for faller Estimate	Standard error	95% CI
HypoD defined as 25OHD <30 ng mL^{-1}								
Holick *et al.* [12]	1488	860	444 (51.6)	628	329 (52.4)	0.97	1.11	0.79; 1.19
Snijder *et al.* [14]	1231	405	323 (79.8)	826	683 (82.7)	0.82	1.17	0.61; 1.12
Beauchet *et al.* [21]	411	135	124 (91.9)	276	233 (84.4)	2.08	1.43	1.04; 4.18
Annweiler *et al.* [24]	329	80	70 (87.5)	249	228 (91.6)	0.65	1.50	0.29; 1.43

Note 25OHD, 25-hydroxyvitamin D; CI, confidence interval.

Appendix: 5

Funnel plot with pseudo 95% confidence limits for studies on serum concentration of 25-hydroxyvitamin D in fallers and nonfallers.



SE: standard error.

