Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized Control Trials

Effect of monthly vitamin D on diverticular disease hospitalization: Post-hoc analysis of a randomized controlled trial

Zhenqiang Wu [a, b], Joanna Broad [b], John Sluyter [a], Debbie Waayer [a], Carlos A. Camargo Jr. [c], Robert Scragg [a, *]

[a] School of Population Health, University of Auckland, Auckland, New Zealand
[b] Department of Geriatric Medicine, University of Auckland, Auckland, New Zealand
[c] Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 16 July 2020
Accepted 23 August 2020

Keywords:
Vitamin D
Supplementation
Diverticular disease
Randomized controlled trial

SUMMARY

Background & aims: Some studies have linked low vitamin D status and high risk of diverticular disease, but the causal relationship between vitamin D and diverticular disease remains unclear; clinical trial data are warranted. The objective was to assess the efficacy of vitamin D_3 supplementation on diverticular disease hospitalization.

Methods: Post-hoc analysis of a community-based randomized double-blind placebo-controlled trial (RCT) with 5108 participants randomized to receive monthly 100,000 IU vitamin D (n = 2558) or identical placebo (n = 2550). The outcome was time to first diverticular disease hospitalization from randomization to the end of intervention (July 2015), including a prespecified subgroup analysis in participants with baseline deseasonalized 25-hydroxyvitamin D (25(OH)D) levels < 50 nmol/L.

Results: Over a median of 3.3 years follow-up, 74 participants had diverticular disease hospitalization. There was no difference in the risk of diverticular disease hospitalization between vitamin D supplementation (35/2558 = 1.4%) and placebo (39/2550 = 1.5%) groups (adjusted hazard ratio (HR) = 0.90; p = 0.65), although in participants with deseasonalized 25(OH)D < 50 nmol/L (n = 1272), the risk was significantly lower in the vitamin D group than placebo (HR = 0.08, p = 0.02).

Discussion: Monthly 100,000 IU vitamin D_3 does not reduce the risk of diverticular disease hospitalization in the general population. Further RCTs are required to investigate the effect of vitamin D supplementation on the diverticular disease in participants with low 25(OH)D levels.

1. Introduction

Diverticular disease is one of the most common gastrointestinal indications for hospital admissions [1]. In the past decade, the incidence of diverticular disease hospitalization has increased, especially in young men [2,3], and management of diverticular disease remains an important challenge [4]. Geographical and seasonal variations have led to the hypothesis that low vitamin D status is associated with increased risk of diverticular disease [5]. This hypothesis was supported by results from a retrospective cohort study [6], which found that higher serum 25-hydroxyvitamin D (25(OH)D) levels in patients with the uncomplicated diverticular disease were associated with a lower risk of diverticular disease hospitalization. However, due to the observational design and limited research on this topic, the causal relationship between vitamin D and diverticular disease remains unclear; clinical trial data are warranted. Our objective was to investigate the effect of monthly 100,000 IU vitamin D_3 supplementation on diverticular disease hospitalization in a post-hoc analysis of a community-based randomized double-blind placebo-controlled trial (RCT). Given the emerging evidence that vitamin D is mainly beneficial in people with vitamin D deficiency [7], we included a pre-specified outcome that vitamin D supplementation prevented diverticular disease hospitalization in participants with vitamin D deficiency.

* Corresponding author. School of Population Health, University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand. Fax: +64 9 3737 503.
E-mail address: r.scragg@auckland.ac.nz (R. Scragg).

https://doi.org/10.1016/j.clnu.2020.08.030
0261-5614/

2. Material and methods

In the Vitamin D Assessment (ViDA) study, 5110 community-dwelling participants in Auckland, New Zealand, were randomly assigned to take a monthly capsule by mail with either 100,000 IU vitamin D_3 or identical placebo, and were followed-up for a median of 3.3 years during 2011–2015. Inclusion criteria were: 1) age 50–84 years; 2) ability to give informed consent; 3) resident in Auckland at recruitment; and 4) anticipated residence in New Zealand for the 4 years study period. Exclusion criteria were: 1) current use of vitamin D supplements (age 50–70 years: > 600 IU/d; 71–84 years: > 800 IU/d); 2) having a psychiatric disorder which prevented participation in the study; 3) history of hypercalcemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery; 4) enrolled in another study which could affect participation in the vitamin D study; and 5) baseline serum calcium > 2.50 mmol/L. Details of the study protocol and main results have been published [8–11]. Approval was given by the New Zealand Multi-region Ethics Committee (MEC/09/08/082/AM) and all participants gave informed consent. The study was registered with the Australian and New Zealand Clinical Trials Register (ACTRN12611000402943).

Baseline characteristics, including sociodemographic, lifestyle, vitamin D or calcium supplements, and medical history diagnosed by a doctor were collected at baseline interview. A 25 ml non-fasting blood sample was collected for immediate measurement of serum calcium, with the remaining remainder for later measurement of serum 25(OH)D concentrations. Serum 25(OH)D concentrations (combining 25(OH)D_2 and 25(OH)D_3) at baseline in all participants were measured using liquid chromatography-tandem mass spectrometry 180 (LC-MS/MS, AB Sciex API 4000, Framingham, MA) by a local laboratory participating in the Vitamin D External Quality Assessment Scheme (DEQAS) program (the inter-assay coefficient of variation for the assay is 12.7% at levels of 25–50 nmol/L and 8% at 100 nmol/L). Deseasonalized (season-adjusted) 25(OH)D values were estimated for each participant by removing a sinusoidal component from baseline 25(OH)D values of all participants [12].

Following the baseline assessment, participants received one placebo capsule (blind to participants) and a "run-in" questionnaire. They were randomly allocated to receive either vitamin D_3 (100,000 IU) or identical placebo (by Tishcon Corporation, Westbury, New York, USA) if they the questionnaire was returned within 4 weeks and confirmed they had taken the capsule. The computer-generated randomization list was managed by a statistician not involved in outcome data collection within randomly assigned blocks of 8, 10, or 12, and stratified by 5-year age groups and ethnic categories. All investigators and participants were blinded until the end of the intervention period (July 2015). The initial mailing had two capsules of vitamin D_3 (200,000 IU) or placebo, followed by one monthly capsule of vitamin D_3 (100,000 IU) or placebo until July 2015. The capsule was mailed to participants monthly until November 2013. After that, for budgetary reasons, four capsules were mailed every four months, along with monthly reminders until July 2015.

All New Zealand residents are allocated a unique National Health Index (NHI) number by the Ministry of Health (MoH), allowing linkage to the National Minimum Dataset (containing public and private hospital discharge information) [13]. The post-hoc outcome was the time to first diverticular disease hospitalization from randomization until July 2015. Diverticular disease hospitalization was defined as primary or secondary hospital discharge diagnosis using the International Statistical Classification of Diseases and Health Related Problems, 10th Revision (ICD-10) diagnosis codes K57.0-K57.9 [14].

The effect of vitamin D supplementation (versus placebo) was examined all participants and the following groups: participants with baseline deseasonalized 25(OH)D levels < 50 nmol/L, no history of diverticular disease hospitalizations during the two years before randomization, and the latter with baseline deseasonalized 25(OH)D levels < 50 nmol/L. All the post-hoc outcome and subgroups were pre-specified before data analyses. Cox proportional hazards regressions (adjusted for age, sex, and ethnicity at randomization) were used to compare the time to first diverticular disease hospitalization in the two treatment groups, with deaths censored (SAS version 9.4, SAS Institute Inc., Cary, NC, USA). A two-sided $p < 0.05$ was considered statistically significant. Based on an overall cumulative incidence of 1.5% in the placebo group (39 participants for the primary outcome), the study had more than 80% power to detect a risk ratio of 0.45 at 5% significance level [15].

3. Results

From all 5110 participants randomized, two withdrew consent, leaving 5108 who were randomized to vitamin D_3 supplementation (n = 2558) or placebo (n = 2550) (Fig. 1). For demographic variables, 2969 (58%) were male, and 4253 (83%) were of European/Other ethnicity, with the remainder being Māori (5.3%), Pacific (6.5) or South Asian (4.9%). The mean (SD) age was 66 (8) years and deseasonalized 25(OH)D was 66 (22) nmol/L. In the two years before randomization, 43 (0.8%) participants had a diverticular disease hospitalization (Table 1).

Over a median follow-up of 3.3 years, there were 74 (1.4%) participants with a diverticular disease hospitalization. There was no difference in the percentage with a diverticular disease hospitalization during study follow-up between the vitamin D (35/2558 = 1.4%) and placebo (39/2550 = 1.5%) groups (adjusted hazard ratio (HR) = 0.90; 95%CI = 0.57–1.14, p = 0.65) (Table 2 & Fig. 2). Similar non-significant results were seen in 5065 participants without a history of diverticular disease hospitalization (HR = 0.97, 95%CI = 0.60–1.57, p = 0.91). However, in 1272 participants with deseasonalized 25(OH)D levels < 50 nmol/L (test for an interaction between binary 25(OH)D levels and treatment effect, p = 0.01), there was a significantly lower percentage of participants with a diverticular disease hospitalization in the vitamin D group (1/613 = 0.1%) compared to placebo (13/659 = 2.0%) (HR = 0.08, 95%CI = <0.01–0.40, p = 0.02). A similar lower risk was observed in participants without a history of diverticular disease hospitalization and with deseasonalized 25(OH)D levels < 50 nmol/L (n = 1264, HR = 0.09, p = 0.03) (Table 2 & Fig. 2).

To provide a better understanding of the findings from the prespecified participants with baseline deseasonalized 25(OH)D levels < 50 nmol/L, we also examined the association between ethnicity and the risk of first diverticular disease hospitalization. In the follow-up period, 14 out of 1272 participants had a diverticular disease hospitalisation, most of whom were of European/Other ethnicity (n = 11), followed by Maori (n = 2) and South Asian (n = 1). Compared to European/Other ethnicity, Maori participants had a higher hazard of diverticular disease hospitalization (adjusted HR = 3.27, 95%CI = 0.50–12.47), and South Asian participants had a slightly lower hazard (adjusted HR = 0.83, 95% CI = 0.04–4.46), but neither finding was significant (p > 0.05) (Table S1).

4. Discussion

This post-hoc analysis of a large community-based RCT indicates that monthly bolus vitamin D_3 supplementation (compared with placebo) does not prevent diverticular disease hospitalization in all participants, nor in participants without a history of diverticular

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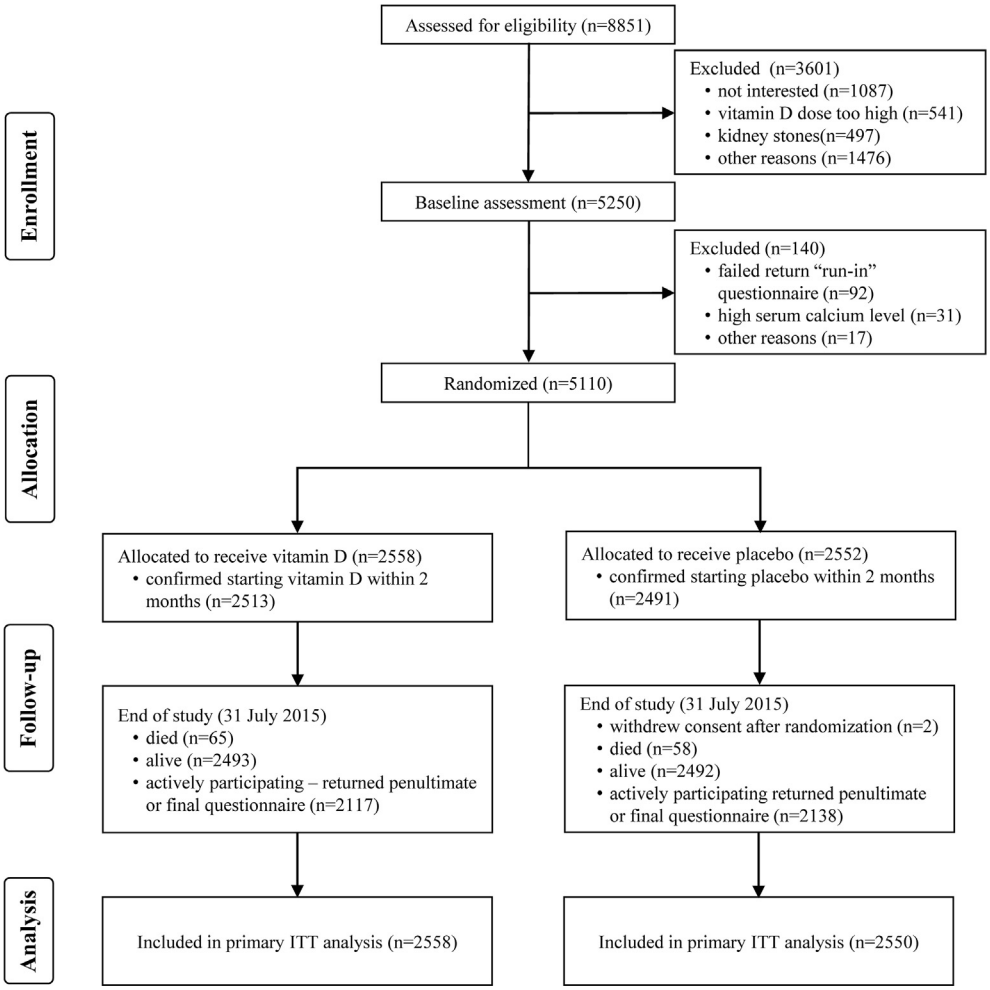

Fig. 1. CONSORT flow diagram in the Vitamin D Assessment study.

Table 1
Baseline characteristics of eligible participants in the Vitamin D Assessment study.

Variables	Vitamin D (n = 2558)	Placebo (n = 2550)
Age (y), mean (SD)	65.9 (8.3)	65.9 (8.3)
Sex, n (%)		
Male	1512 (59.1)	1457 (57.1)
Female	1046 (40.9)	1093 (42.9)
Ethnicity, n (%)		
European/Other	2127 (83.2)	2126 (83.4)
Māori	137 (5.4)	135 (5.3)
Pacific	168 (6.6)	166 (6.5)
South Asian	126 (4.9)	123 (4.8)
DD history (2 years before randomization), n (%)		
Yes	25 (1.0)	18 (0.7)
No	2533 (99.0)	2532 (99.3)
25(OH)D (nmol/L), mean (SD)	66.4 (22.5)	65.7 (22.5)
25(OH)D (nmol/L), n (%)		
0–49.9	659 (25.8)	613 (24.0)
≥50.0	1891 (74.2)	1945 (76.0)

DD, diverticular disease hospitalization; SD, standard deviation; 25(OH)D, deseasonalized 25-hydroxyvitamin D levels.

disease hospitalization. However, there was a statistically significant benefit in participants who had a deseasonalized 25(OH)D < 50 nmol/L (a pre-specified subgroup). These findings partly support the hypothesis from previous observational studies of a role for vitamin D status in the pathogenesis of the diverticular disease. For example, a retrospective cohort of 10,038 patients with diverticular disease found lower 25(OH)D levels in patients who required hospitalization (RR = 0.49, 95%CI = 0.38–0.62) [6]. Likewise, a national study of 226,522 non-elective hospital admissions found a higher rate of diverticular disease hospitalizations in areas with low ultraviolet light exposure [5], the major determinant of vitamin D status. A potential pathophysiological mechanism of vitamin D on diverticular disease hospitalisation is the decreased expression of pro-inflammatory cytokines (e.g. IL-6, IL-8, TNF α, CRP) from vitamin D [16].

The significantly reduced risk of diverticular disease hospitalization from vitamin D supplementation observed in the pre-specified subgroup with low 25(OH)D levels is consistent with evidence from previous vitamin D trials. These have noted that the beneficial effects of vitamin D supplementation (on other disease outcomes) are mainly limited to people with vitamin D deficiency [7]. However, in the current study, this subgroup had only 14 diverticular disease hospitalizations after randomization. We acknowledge that the results could be due to chance and require replication in other large RCTs.

Ethnic variations in hospitalization for gastrointestinal disorders, including diverticular disease, were reported by previous studies [17–20]. In these studies, diverticular disease hospitalisation rates were highest in White and followed by Hispanics and Asian/Pacific Islanders. The anatomical location of diverticular disease has been reported to be predominantly in the right colon in

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Table 2
Proportion of participants having a diverticular disease hospitalization during follow-up and hazard ratios adjusting for age, sex, and race/ethnicity.

Diverticular disease hospitalization (ICD-10 code = K57)	No. of events/No. of participants (%)		Adjusted hazard ratio (95%CI), p
	Vitamin D	Placebo	
All (n = 5108)	35/2558 (1.4)	39/2550 (1.5)	0.90 (0.57, 1.42), 0.65
No history of DD (n = 5065)	33/2533 (1.3)	34/2532 (1.3)	0.97 (0.60, 1.57), 0.91
25 (OH)D level < 50 nmol/L (n = 1272)	1/613 (0.1)	13/659 (2.0)	0.08 (<0.01, 0.40), 0.02
No history of DD and 25(OH)D level < 50 nmol/L (n = 1264)	1/609 (0.2)	11/655 (1.7)	0.09 (<0.01, 0.48), 0.03

DD, diverticular disease hospitalization; 25(OH)D, deseasonalized 25-hydroxyvitamin D levels; CI, confidence interval.

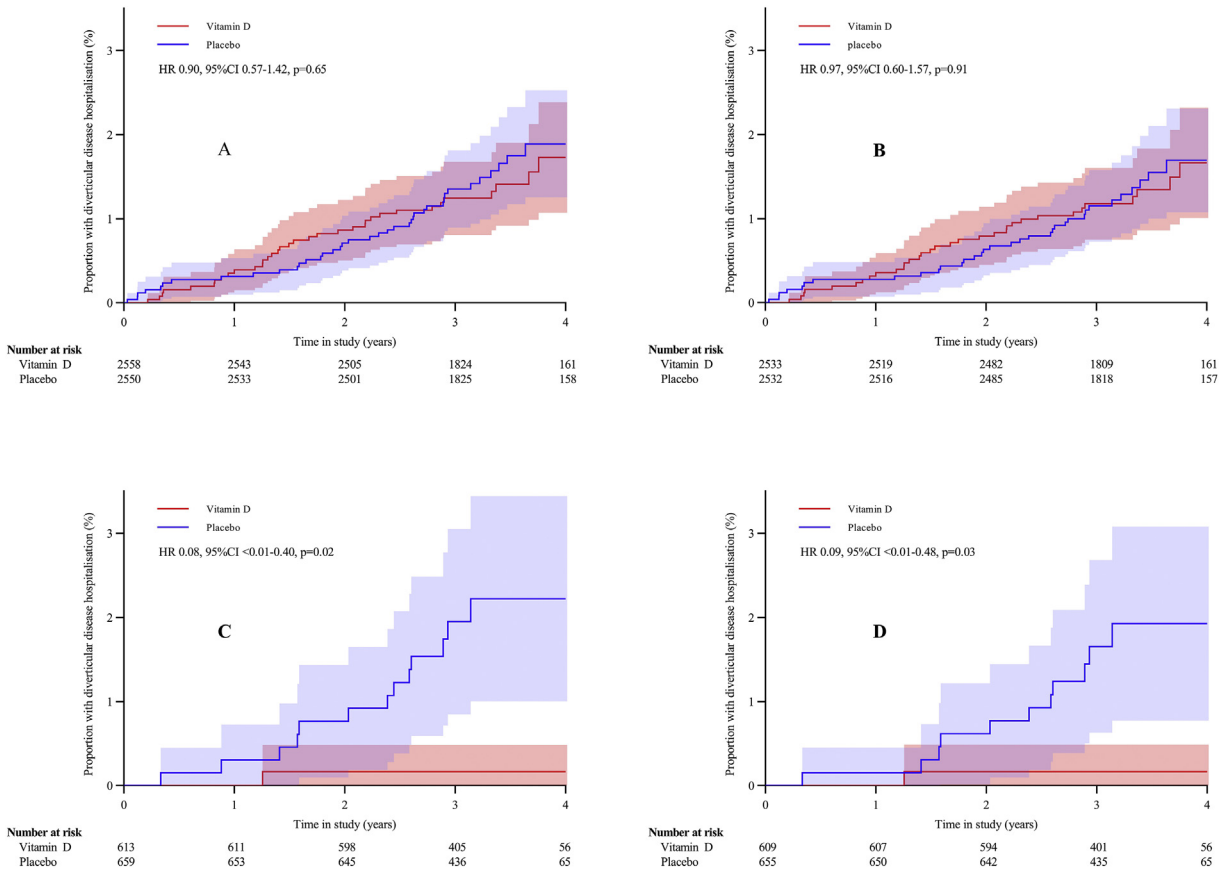

Fig. 2. Proportion with a diverticular disease hospitalization between vitamin D and placebo groups during the median of 3.3 years follow-up. (A: all participants; B: no history of diverticular disease hospitalization participants; C: deseasonalized 25(OH)D levels < 50 nmol/L participants; D: deseasonalized 25(OH)D levels < 50 nmol/L and no history of diverticular disease hospitalization participants).

Asian countries, whereas it is predominantly in the left colon in Western countries [21]. However, due to the small number of participants with diverticular disease hospitalisations in our study, although there was a trend for a higher proportion of diverticular disease hospitalisation observed in Māori (1.9%) and a lower proportion in South Asian (0.6%) compared to European/Other ethnicity (1.3%), we failed to confirm significant ethnic variations of diverticular disease hospitalisation.

The strengths of this study include the community-based study design, high retention (87%) and adherence (84%) rates [22], and relatively long follow-up time (median 3.3 years); although, there were insufficient numbers to analyze recurrent events (10/74). Some limitations should be recognized in our study. First, as diverticular disease hospitalisation was not a specified outcome in the study protocol, and this will increase the likelihood of finding a statistically significant result by chance alone, although this outcome was predefined before analysis. Secondly, while the main significant finding of this study was from a pre-specified analysis of participants with 25(OH)D levels < 50 nmol/L, only a small proportion (25%) of participants were included in the analysis, and only 14 participants (1%) had diverticular disease hospitalizations after randomization. Third, there were only 91 participants (1.8%) with severe vitamin D deficiency (e.g. 25(OH)D levels < 25.0 nmol/L), and this limited a further exploration of the effectiveness of vitamin D in this subgroup in our study. It should be recognised that the statistical power of the subgroup analysis was low, and we did not subject the results to correction for multiple comparisons. Therefore, we acknowledge that these findings may need to be considered exploratory, and studies with larger sample size or meta-analyses are required to replicate the vitamin D effectiveness on diverticular disease for participants with low vitamin D levels.

In summary, we found that monthly 100,000 IU vitamin D_3 supplementation does not reduce risk of diverticular disease hospitalizations in the general population. Further RCTs or individual

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participant data (IPD)-level meta-analysis of RCTs are required to investigate the effect of vitamin D supplementation on diverticular disease in participants with low 25(OH)D levels.

Guarantor of the article

Zhenqiang Wu, PhD & Robert Scragg, PhD.

Specific author contributions

Z.W.: Conceptualization, Visualization, Writing - original draft, Formal analysis, Methodology.

J.B.: Conceptualization, Writing - review & editing, Supervision.

J.S.: Writing - review & editing.

D.W.: Project administration, Writing - review & editing, Investigation.

C.C.: Funding acquisition, Conceptualization, Writing - review & editing.

R.S.: Funding acquisition, Conceptualization, Supervision, Writing - review & editing.

Financial support

Major funding for this study was provided by grant 10/400 from the Health Research Council of New Zealand (R.S. & C.C.) and by the Accident Compensation Corporation of New Zealand.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.08.030.

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