Effect of monthly high-dose vitamin D supplementation on acute respiratory infections in older adults: A randomized controlled trial

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Summary: In a randomized, double-blinded, placebo-controlled trial of >5000 older adults in New Zealand, we found that monthly high-dose vitamin D supplementation did not prevent acute respiratory infection. Whether effects of daily or weekly dosing differ requires further study.

ABSTRACT

Background: Although adults with low vitamin D status are at increased risk of acute respiratory infection (ARI), randomized controlled trials of vitamin D supplementation have provided inconsistent results.

Methods: We performed a randomized, double-blinded, placebo-controlled trial of 5,110 adults, aged 50-84 years. In 2011-2012, participants were randomized to an initial oral dose of 200,000 IU vitamin D3 followed by 100,000 IU monthly (n=2,558) or placebo (n=2,552) until late 2013 (median follow-up 1.6 years). Participants reported upper and lower ARIs on monthly questionnaires. Cox models analyzed time to first ARI (upper or lower) by treatment group.

Results: Participants' mean age was 66 years and 58% were male; 83% were of European/Other ethnicity, with the rest Maori, Polynesian or South Asian. Mean (SD) baseline blood 25-hydroxyvitamin D (25OHD) level was 63 (24) nmol/L; 25% were <50 nmol/L. In a random sample (n=441), vitamin D supplementation increased mean 25OHD to 135 nmol/L at 3 years, while those on placebo stayed at 63 nmol/L. During follow-up, 3,737 participants reported at least one ARI: 74.1% in the vitamin D group versus 73.7% in the placebo group. The hazard ratio for vitamin D compared to placebo was 1.01 (95%CI, 0.94, 1.07). Similar results were seen in most subgroups, including those with baseline 25OHD <50 nmol/L and in analyses of the upper/lower components of the ARI outcome.

Conclusions: Monthly high-dose vitamin D supplementation does not prevent ARI in older adults with a low prevalence of profound vitamin D deficiency at baseline. Whether effects of daily or weekly dosing differ requires further study.

Keywords: vitamin D, supplement, acute respiratory infection, adults, randomized controlled trial

Trial Registration**:** Australian New Zealand Clinical Trials Registry, Identifier ACTRN12611000402943.

INTRODUCTION

Acute respiratory infections (ARIs) are common and have public health impact [1]. While most ARIs are self-limited viral illnesses, they can be fatal, particularly in high-risk groups such as infants and older adults. ARIs of the lower respiratory tract are traditionally linked to bacterial pathogens (e.g., pneumococcal pneumonia) but viral pathogens are most common [2,3]. Although ARIs are often categorized anatomically into upper versus lower respiratory tract infections, ARIs often involve multiple anatomic locations. Influenza virus, for example, can manifest in either location, which raises questions about the value (and reproducibility) of the anatomic distinction. Either way, there currently are limited strategies to prevent most ARIs.

For more than a decade, many studies have linked low vitamin D status with increased risk of ARI [4]. Vitamin D status is best measured with blood levels of 25-hydroxyvitamin D (25OHD). In recent years, randomized controlled trials (RCTs) have investigated the role of vitamin D supplementation in ARI prevention. While some studies have shown substantial benefit [5], others have not [6]. This heterogeneity was investigated in a recent individual participant data (IPD) meta-analysis of 25 RCTs involving approximately 11,000 participants [7]. The major conclusions of this international collaboration were that vitamin D supplementation is safe and protects against ARI in two subgroups of the general population: those with low baseline 25OHD levels and those who receive non-bolus (i.e., daily or weekly) supplement dosing.

The present RCT was initiated in 2011 before completion of our New Zealand trial showing no ARI benefit among adults given monthly vitamin D supplementation [6], and the 2017 IPD meta-analysis [7]. We concluded at the time that a monthly mailed dose would provide a sustained increase in 25OHD, plus logistical and cost advantages over daily dosing. Accordingly, the current trial investigated the effect of monthly high-dose vitamin D supplementation in the prevention of ARI among >5,000 older adults.

METHODS

Participants

This RCT is a pre-specified analysis of the ViDA (Vitamin D Assessment) study, a randomized, double-blinded, placebo-controlled trial of the effect of monthly high-dose vitamin D supplementation on health outcomes, with a primary outcome of cardiovascular disease [8] and major secondary outcomes of ARI (current article) and falls/fractures [9]. Inclusion criteria were men and women from family practice registers and community groups, aged 50-84 years and resident in Auckland at the time of their recruitment. Exclusion criteria included: 1) diagnosis of a terminal illness or in hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of >600 IU daily if aged 50-70 years or >800 IU daily if aged 71-84 years, 4) history of renal stones, hypercalcemia, or medical conditions that can cause hypercalcemia, and 5) baseline serum calcium >10.0 mg/dL.

Screening and baseline measurements took place at the University of Auckland between 2011 and 2012, with 5,110 participants randomized (using computer generation) to

receive either vitamin D or placebo. Random assignment to one of the two treatment groups was made with random block sizes of 8, 10 or 12, within ethnic and 5-year age groups. As each participant became eligible for randomization, the next sequential treatment within their ethnic/age strata was allocated. The randomization process was supervised by the study biostatistician (AWS) to ensure that participants and staff who collected the data were blinded to allocation. Ethics approval was provided by the Multi-region Ethics committee (MEC/09/08/082). Written, informed consent was obtained from each participant. This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000402943). Full study design details have been published elsewhere [10].

Vitamin D Intervention

Vitamin D_3 (100,000 IU (2.5 mg)) or placebo softgel oral capsules, sourced from Tishcon Corporation (Westbury, NY), were mailed to participants' homes. Two capsules were sent in the first mail-out after randomization (i.e., a 200,000 IU bolus, or placebo, at the start of the intervention period), followed by a monthly 100,000 IU (daily dose equivalent ~3300 IU/day) capsule of vitamin D_3 (or placebo) throughout the remainder of the trial. To achieve masking, the vitamin D and placebo capsules were identical in appearance.

ARI Outcome

The primary outcome was time to first reported ARI, which was a combination of upper respiratory infection (URI) and lower respiratory infection (LRI) events. Respiratory infections were captured every month through the mailed questionnaire, which asked

about recent URI ("cold, runny nose, sore throat or flu-like illness") and recent LRI ("chest infection [pneumonia or acute bronchitis]"). The URI and LRI components were analyzed individually as secondary outcomes.

Follow-up for the ARI analysis focused on May 1, 2011 to November 1, 2013 when, for financial reasons, the original 1-monthly mailings were changed to 4-monthly until the end of overall ViDA follow-up on July 1, 2015. Although participants received monthly reminders to take the assigned capsule each month during the 4-monthly phase of the trial, the revised questionnaire assessed outcomes (including ARI) across the entire 4-month interval. In the present analysis, we focused on the first (1-monthly) phase of the trial because we did not want to combine ARI assessment by monthly questionnaire with the less precise assessment at 4-month intervals.

Other Variables

All measurements were carried out by trained staff using a standardized protocol. Interviewer-administered questionnaires were used to collect baseline data on age, sex, ethnicity (defined by self-identification), smoking, number of colds in past year, and medical history. Without shoes and in light clothing, height (±0.1 cm) was measured with a stadiometer, and weight (±0.1 kg) with digital scales. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Participants were considered to have asthma if they reported doctor-diagnosed asthma and had recently used an inhaled asthma medication. Participants were considered to have chronic obstructive pulmonary disease (COPD) if they were current- or ex-smokers and had a forced expiratory volume in 1-second (FEV1) / forced vital capacity

(FVC) ratio of <0.7. Further details of the spirometry testing have been published elsewhere [11].

Blood samples were collected at baseline from all participants (and also at 6-, 12-, 24-, and 36-month follow-up from a randomly-selected sample of 441 participants) to test for hypercalcemia (corrected calcium >10.4 mg/dL). Remaining plasma aliquots were stored frozen at -80°C. Serum 25OHD (combining D_2 and D_3) concentration was measured in these aliquots (baseline and follow-up samples were measured in the same batch for each participant) by liquid chromatography-tandem mass spectrometry (ABSciex API 4000, Framingham, MA) at a laboratory participating in the Vitamin D External Quality Assessment Scheme (DEQAS) program (www.deqas.org).

Statistical analysis

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). On an intention-to-treat basis, participants in the two randomly-allocated groups were described using standard descriptive statistics. Clinical outcomes then were compared using Cox proportional hazards model. We censored individuals during follow-up. For participants who did not report an ARI, we treated deaths during follow-up as censored observations.

To address any potential concern about our decision to focus on ARI outcomes from the 1-monthly phase of data collection (2011-2013), we repeated analyses across the entire follow-up period (2011-2015) and results did not materially differ (see Supplementary Table 1).

For the adherence analysis of blood 25OHD levels over time, general linear mixed models were used to assess the effect of vitamin D supplementation with repeated

time incorporated using an unstructured correlation structure, using PROC MIXED. This analysis method handles missing data by fitting a statistical model over all available observations without introducing bias.

Deseasonalized (season-adjusted) baseline 25OHD levels were calculated for each participant from the mid-point between the estimated maximum and minimum 25OHD levels over a calendar year, from their individual measured baseline 25OHD and date of blood collection, using a sinusoidal model with parameters derived from baseline values for all participants in the main ViDA study [12]. We defined vitamin D deficiency as having a deseasonalized 25(OH)D of <50 nmol/L [12].

Aside from performing analysis among all eligible participants (total sample), we decided *a priori* to conduct subgroup analyses among participants with baseline vitamin D deficiency (<50 nmol/L), and by major demographic groups. We also examined pre-specified subgroups defined by baseline BMI, smoking status, number of colds in past year, and having asthma or COPD.

The ViDA study was originally powered to detect a clinically relevant reduction in cardiovascular events (primary outcome), as described elsewhere [10]. For the current analysis, given the study cumulative event rate of 74% in the placebo group (1,882 events in 2,539 people), an accrual time of 19 months and a total follow-up time of 2.5 years, at the 5% significance level, the ViDA study could detect (in the total sample) a hazard ratio of 0.90 for the primary outcome (upper and lower ARI combined) with 80% power – and a hazard ratio of 0.89 with 90% power.

P-values were not corrected to account for the multiple hypothesis tests because, given the known heterogeneity in the effectiveness of vitamin D supplementation in ARI

prevention [4], we did not want to miss any potentially important findings [13]. A two-sided P<0.05 was considered statistically significant.

RESULTS

Figure 1 shows the CONSORT diagram for this ARI analysis. Briefly, 47,905 individuals were invited, of which 8,851 were assessed for eligibility and 5,250 underwent the baseline interview. After 140 exclusions, there were 5,110 participants available for randomization. Two individuals withdrew consent and 52 did not return a single questionnaire during follow-up; these 54 individuals were removed, thereby leaving an analytic sample of 5,056. The mean age of the ViDA participants was 66 years and 58% were male; 83% were of European/Other ethnicity, with the remaining 17% Maori, Polynesian, or South Asian. **Table 1** shows balance between the two randomly-allocated groups across multiple dimensions, including vitamin D status, demographics, and other ARI-related variables.

Adherence-related data support fidelity to the protocol. For example, 97% of participants reported taking the study capsule during the final (November 2013) monthly mail-out period. Likewise, in the random subset of 441 participants who underwent multiple blood testing as part of a safety evaluation, we found further evidence of high fidelity. **Figure 2** shows the observed blood 25OHD levels over time, by assigned group, with the blood 25OHD level of the intervention group going from 63 nmol/L to 135 nmol/L, consistent with their vitamin D supplementation, while the 25OHD in the placebo group did not change. Participant retention also was high; for example, 87% of

participants returned the final monthly questionnaire (November 2013). Lastly, the vitamin D intervention did not affect participant-reported adverse events [14,15].

Table 2 shows the primary outcome (time to first ARI event) in the overall group, along with this same outcome in pre-specified subgroups. Over a median of 1.6 years of follow-up, 3,737 participants reported at least one ARI: 74.1% in the vitamin D group compared to 73.7% in the placebo group. The adjusted hazard ratio (aHR) for ARI for vitamin D compared to placebo was 1.01 (95%CI, 0.94, 1.07). The primary outcome data are shown graphically in **Figure 3**, which confirms the lack of any apparent benefit. With regard to the subgroups, there was no evidence of benefit among individuals with baseline 25OHD <50 nmol/L. Similar results also were seen in separate analyses of the upper and lower components of the primary (overall) ARI outcome (Table 2) and for a more detailed classification of asthma and COPD (see Supplementary Tables 2 and 3).

One possible exception was current smokers (n=314), where vitamin D supplementation appeared to reduce ARI by approximately 25% (P-interaction=0.03). This overall ARI reduction was driven by a decrease in time to URI (n=222 events; aHR 0.71; 95%CI, 0.54-0.93). There was no between-group difference in time to LRI (n=81 events; aHR 1.12; 95%CI, 0.72-1.73).

To provide better context for these mostly null findings, we also examined the *observational* (non-interventional) association between baseline 25OHD levels and future risk of ARI in the placebo group only. As expected, we found a significant inverse association similar to that reported in many prior cohort studies [4]. Compared to participants with a baseline 25OHD level in the highest quartile, individuals with progressively lower 25OHD levels experienced progressively higher risk of ARI: 3rd

quartile with aHR 1.07 (95%CI, 0.92-1.25), 2nd quartile with 1.19 (95%CI, 1.03-1.39), and lowest quartile with 1.21 (95%CI 1.03-1.42); P_{trend} <0.05.

DISCUSSION

Monthly high-dose vitamin D supplementation did not prevent ARI in this population of older New Zealand adults. The lack of effect was apparent in all major subgroups, including individuals with blood 25OHD <50 nmol/L at baseline, and in separate analyses of the URI and LRI components. One possible exception was current smokers, where monthly vitamin D supplementation may have reduced ARI by 25%.

The RCT has several important strengths. First, the sample size and duration were substantially larger than prior RCTs. The statistical power of our trial was sufficient to detect a 10% decrease in the intervention group, which is substantially less than the 50% benefit reported in prior RCTs [4]. Second, adherence data supports fidelity to the protocol, including confirmation that the intervention group experienced a significant boost in their 25OHD level, while the placebo group did not. Third, retention was high (>80%). Lastly, a *post hoc* observational analysis of the placebo group confirmed the expected association between baseline 25OHD level and future risk of ARI – i.e., this population-based sample could have shown the hypothesized benefit from vitamin D supplementation.

The RCT also had some important limitations. First, the IPD meta-analysis by Martineau and colleagues identified individuals with severe vitamin D deficiency (baseline levels of <25 nmol/L) as more likely to obtain ARI benefits [7]. Because ViDA had only 89 participants with severe vitamin D deficiency, we could not adequately test for benefit in this *post-hoc* subgroup. Second, we did not confirm the ARI outcome with

clinical examination, viral testing, or chest films but this imprecision is common in population-based ARI research and should have affected the intervention and placebo groups equally. Moreover, this imprecision in the clinical outcome has not obscured prior studies with much smaller samples that observed benefits from non-bolus (i.e., daily or weekly) dosing in vitamin D deficient populations [4]. Third, we tested a specific intervention (vitamin D supplement bolus of 200,000 IU at baseline, then 100,000 IU monthly thereafter) in a specific population (older adults). The relevance of these data to other interventions in different populations (e.g., daily dosing in children) is unclear.

Based on humans' frequent exposure to the sun, one can easily intuit that more frequent dosing (e.g., daily or weekly dosing) is more likely to mimic the natural production of vitamin D in the body. This more "physiologic" pattern may be the most likely to confer health benefits. Indeed, the IPD meta-analysis of approximately 11,000 trial participants [7] supports this conclusion, with ARI benefits limited to those: 1) with low baseline levels of 25OHD, and 2) who did not get their vitamin D supplementation in bolus (e.g., monthly) doses. Our new RCT results are consistent with the IPD meta-analysis. With the upcoming addition of >5000 ViDA participants, it seems very unlikely that the null finding for bolus dosing will change in the years ahead.

The explanation for why monthly (bolus) dosing does not prevent ARI – but daily or weekly dosing does [7] – remains uncertain. Although vitamin D requires activation to the hormonal form (1,25-dihydroxyvitamin D) to achieve full biological activity, some investigators hypothesize that both intact vitamin D (circulating half-life of 12-24 hours) and 25OHD (circulating half-life of 2-3 weeks) are important in the activation process [16]. Optimal functioning of the vitamin D endocrine/autocrine system may require significant,

steady availability of vitamin D to ensure stable circulating concentrations. If true, monthly dosing could lead to different effects on specific clinical outcomes due to the short circulating half-life of intact vitamin D.

Although the current trial was mostly null, there was evidence of benefit among current smokers. This *a priori* analysis was motivated by smokers' increased risk of ARI [17] and prior observations that vitamin D supplementation may have added value in higher-risk groups [18]. The observed benefit was limited to URI. These smoker results parallel our findings on the effects of monthly vitamin D supplementation on lung function [11]. Briefly, vitamin D did not improve lung function in everyone, but benefitted ever-smokers, especially those with vitamin D deficiency or asthma/COPD. Nevertheless, we acknowledge that the ARI results may be due to chance and encourage further research to replicate (or refute) this subgroup finding.

Recent IPD meta-analyses of RCTs on the effects of vitamin D supplementation on asthma exacerbations [19] and COPD exacerbations [20] provide another perspective. While these IPD meta-analyses also showed that individuals with lower baseline 25OHD levels are more likely to obtain benefit, interestingly, they found that dosing frequency did not matter. In other words, even monthly vitamin D doses benefitted asthma and COPD patients with baseline 25OHD levels of <25 nmol/L. This apparent discordance between the effects of vitamin D supplementation on ARI *per se* versus on asthma/COPD exacerbations merits further study. It raises the intriguing possibility that, while viral infections trigger most asthma/COPD exacerbations, the beneficial effects of vitamin D on asthma/COPD exacerbations may be involve other effects, such as anti-inflammatory actions [21] – even when the vitamin D is taken in bolus doses. Although ViDA is

underpowered to look at the effect of vitamin D supplementation on asthma/COPD exacerbations among older adults with vitamin D deficiency, we look forward to contributing these data to future IPD meta-analyses [19,20]. Either way, these emerging data suggest that the three outcomes (ARI, asthma exacerbation, and COPD exacerbation) are not interchangeable.

In summary, this population-based RCT of >5,000 older adults showed that monthly high-dose vitamin D supplementation did not prevent ARI. One subgroup (current smokers) showed benefit but this isolated finding requires replication. More importantly, further study is needed to determine whether the effects of daily or weekly dosing differ. The recent completion of the US-based VITAL trial (n=25,874) [22] will provide another opportunity to test whether daily vitamin D dosing (2000 IU/day) protects against ARI, particularly among individuals with low vitamin D status. In the meantime, we do not recommend monthly dosing of vitamin D for the prevention of ARI.

NOTES

ACKNOWLEDGMENT

We thank the participants and the ViDA study staff for their outstanding contributions.

FUNDING

This work was supported by the Health Research Council of New Zealand [grant 10/400]; and the Accident Compensation Corporation of New Zealand. The sponsors had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; nor preparation, review or approval of the manuscript.

Potential conflicts of interest:

Carlos A. Camargo, Jr. – No conflict.

John Sluyter – No conflict.

Alistair W. Stewart – No conflict.

Kay-Tee Khaw – No conflict.

Carlene M.M. Lawes – No conflict.

Les Toop – No conflict.

Debbie Waayer – No conflict.

Robert Scragg – No conflict.

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Table 1. Baseline characteristics of 5,056 participants, by treatment group

Variable*	**Vitamin D** n=2,539	**Placebo** n=2,517
	mean (SD) or n (%)	
Blood 25-hydroxyvitamin D (nmol/L)		
Observed	63.7 (23.6)	63.0 (23.5)
Deseasonalized	66.5 (22.5)	65.9 (22.5)
Deseasonalized <50 nmol/L	602 (24)	645 (26)
Deseasonalized <25 nmol/L	45 (2)	44 (2)
Age (years)	66.4 (8.3)	66.4 (8.3)
Male sex	1,500 (59)	1,435 (57)
Ethnicity		
European/Other	2,119 (83)	2,110 (84)
Maori	134 (5)	127 (5)
Pacific	161 (6)	157 (6)
South Asian	125 (5)	123 (5)
Body mass index (kg/m^2)	28.3 (5.1)	28.5 (4.9)
Smoking		
Never	1,277 (50)	1,304 (52)
Past	1,093 (43)	1,056 (42)
Current	162 (6)	152 (6)
≥1 cold in past year	940 (37)	899 (36)
Asthma	340 (13)	352 (14)

COPD	336 (13)	296 (12)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

* Numbers/percentages do not total 100% due to missing or "don't know" responses.

Table 2. Proportion of participants with acute respiratory infection during follow-up, by treatment group; and adjusted hazard ratios (placebo as reference)

Outcome and Study Population		Vitamin D (n=2,539)	Placebo (n=2,517)	Adjusted Hazard Ratio (95%CI)*	P-value
		# events (%)			
Acute Respiratory Infection					
All participants		1,882 (74)	1,855 (74)	1.01 (0.94-1.07)	0.85
A priori baseline subgroups:					
- 25OHD†	<50 nmol/L	444 (74)	460 (71)	1.08 (0.95-1.23)	0.27
	≥50 nmol/L	1,437 (74)	1,394 (75)	0.99 (0.92-1.06)	0.75
- Age	50-64.9 years	717 (72)	721 (73)	1.01 (0.91-1.12)	0.89
	65-74.9 years	868 (77)	863 (77)	0.98 (0.90-1.08)	0.74
	≥75 years	297 (72)	271 (67)	1.11 (0.94-1.30)	0.24
- Sex	Male	1,071 (71)	1,020 (71)	1.00 (0.92-1.09)	0.98
	Female	811 (78)	835 (77)	1.02 (0.92-1.12)	0.75
- Ethnicity	European/other	1,590 (75)	1,572 (75)	1.00 (0.94-1.08)	0.91
	Maori	104 (78)	103 (81)	0.97 (0.74-1.28)	0.83
	Pacific	103 (64)	105 (67)	0.93 (0.70-1.22)	0.59
	South Asian	85 (68)	75 (61)	1.24 (0.90-1.69)	0.19
- BMI	<25 kg/m^2	446 (72)	424 (72)	0.94 (0.83-1.08)	0.39
	25-29.9 kg/m^2	835 (73)	837 (73)	1.02 (0.92-1.12)	0.75
	≥30 kg/m^2	600 (78)	594 (75)	1.06 (0.94-1.19)	0.34

- Smoking‡	Never	959 (75)	939 (72)	1.06 (0.97-1.16)	0.20
	Past	810 (74)	791 (75)	0.99 (0.90-1.09)	0.83
	Current	108 (67)	120 (79)	**0.75 (0.57-0.97)**	**0.03**
- Colds in past year	None	648 (69)	605 (67)	1.05 (0.94-1.18)	0.36
	1-2	1,062 (76)	1,061 (76)	0.99 (0.91-1.08)	0.86
	≥3	160 (85)	175 (83)	1.00 (0.80-1.24)	0.97
- Asthma		282 (83)	282 (80)	1.03 (0.88-1.22)	0.70
- COPD		252 (75)	233 (79)	0.91 (0.76-1.09)	0.31
Secondary outcomes					
Upper respiratory infection		1,827 (72)	1,797 (71)	1.01 (0.94-1.07)	0.86
Lower respiratory infection		477 (19)	462 (18)	1.03 (0.90-1.17)	0.70

Abbreviation: 95%CI, 95% confidence interval; 25OHD, 25-hydroxyvitamin D; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

* Adjusted for age, sex, and ethnicity

† Based on deseasonalized 25OHD levels (see Methods)

‡ P for interaction = 0.03

FIGURE LEGENDS

Figure 1. Flow diagram for the ViDA Study.

Figure 2. Observed blood 25-hydroxyvitamin D (25OHD) concentration (mean ± 95% confidence interval; in nmol/L) in the random sample at baseline and at the 6-, 12-, 24-, and 36-month follow-up visits, by treatment group.

Figure 3. Cumulative incidence plot for acute respiratory infection by treatment group. Thin outer lines represent 95% confidence intervals.

Figure 1

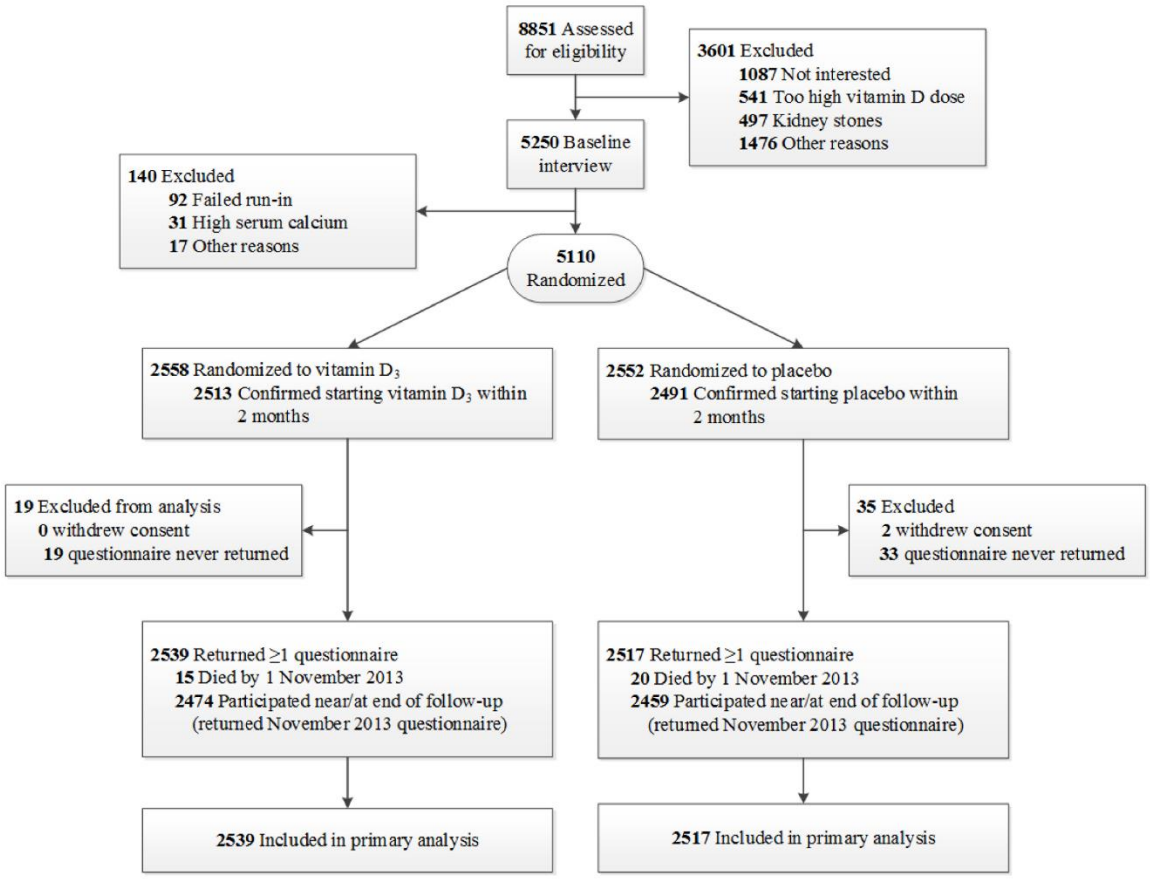


Figure 2

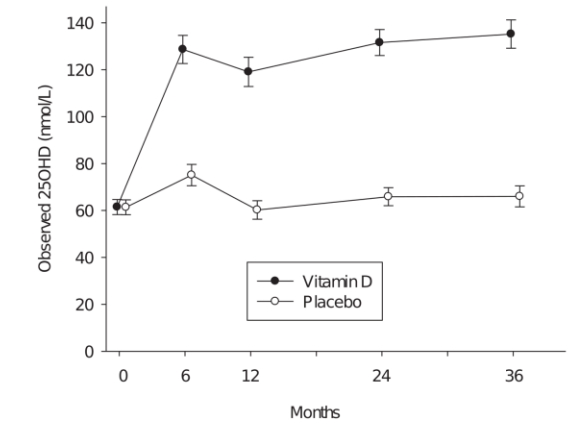
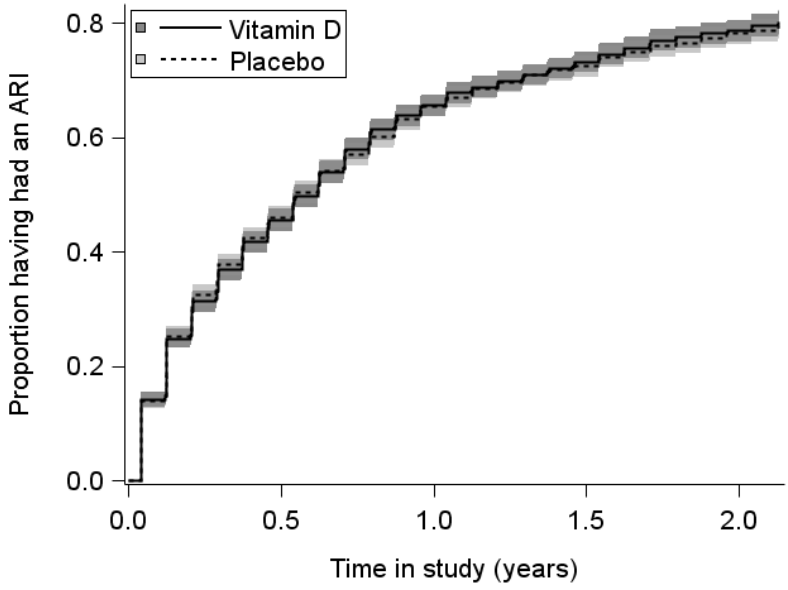


Figure 3



No. at risk					
Vitamin D	2539	1357	830	353	125
Placebo	2517	1341	819	357	129