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Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial

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ABSTRACT

Background: Depressive symptoms and impaired physical functioning are prevalent among older adults. Supplementation with vitamin D might improve both conditions, particularly in persons with low vitamin D status.

Objective: The D-Vitaal study primarily aimed to investigate the effect of vitamin D supplementation on depressive symptoms, functional limitations, and physical performance in a high-risk older population with low vitamin D status. Secondary aims included examining the effect of vitamin D supplementation on anxiety symptoms, cognitive functioning, mobility, handgrip strength, and health-related quality of life.

Methods: This study was a randomized placebo-controlled trial with 155 participants aged 60–80 y who had clinically relevant depressive symptoms, ≥1 functional limitations, and serum 25-hydroxyvitamin D [25(OH)D] concentrations of 15–50/70 nmol/L (depending on season). Participants received 1200 IU/d vitamin D_3 ($n = 77$) or placebo tablets ($n = 78$) for 12 mo. Serum 25(OH)D was measured at baseline and 6 mo; outcomes were assessed at baseline, 6 mo, and 12 mo. Linear mixed-models analyses were conducted to assess the effect of the intervention.

Results: The supplementation increased serum 25(OH)D concentrations in the intervention group to a mean ± SD of 85 ± 16 nmol/L compared with 43 ± 18 nmol/L in the placebo group after 6 mo ($P < 0.001$). No relevant differences between the treatment groups were observed regarding depressive symptoms, functional limitations, physical performance, or any of the secondary outcomes.

Conclusions: Supplementation with 1200 IU/d vitamin D for 12 mo had no effect on depressive symptoms and physical functioning in older persons with relatively low vitamin D status, clinically relevant depressive symptoms, and poor physical functioning. This trial is registered with the Netherlands Trial Register (www.trialregister.nl) under NTR3845. *Am J Clin Nutr* 2019;110:1119–1130.

Keywords: vitamin D, 25(OH)D, depressive symptoms, physical functioning, functional limitations, physical performance, older adults, randomized clinical trial, prevention, supplementation

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Supplemental Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: AE, adverse event; BAI, Beck Anxiety Inventory; CES-D, Center of Epidemiological Studies–Depression scale; EQ-5D, EuroQol-5 Dimensions; HR-QoL, health-related quality of life; ITT, intention to treat; MDD, major depressive disorder; RCT, randomized controlled trial; SF-36, Short Form–36 Health Survey; SPPB, Short Physical Performance Battery; TUG, timed up-and-go; VDR, vitamin D receptor; $1,25(OH)_2D$, 1,25 dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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Introduction

Depressive symptoms and poor physical functioning are 2 common and burdensome health conditions among older persons (1–3). Simple and safe prevention strategies for these conditions are lacking. In addition, the prevalence of inadequate vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentrations <50 nmol/L) (4) is high in this population (5, 6).

Previous research has suggested that low vitamin D status may be associated with depressive symptoms as well as decreased physical health, but the many studies in this field have often yielded conflicting results. Although prospective cohort studies suggest that lower vitamin D status is associated with more depressive symptoms (7), functional limitations (8), and poorer physical performance (9), evidence from randomized controlled trials (RCTs) remains inconclusive regarding causality (10).

Biological evidence for the association of vitamin D with depressive symptoms and poor physical functioning is given by the presence of the activating enzyme 1α-hydroxylase (CYP27B1)—which converts 25(OH)D into 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]—and the vitamin D receptor (VDR) in brain areas, such as the hippocampus, hypothalamus, and cerebellum (11, 12), and the presence of 1,25$(OH)_2$D and the VDR in muscle cells (13). Furthermore, 1,25$(OH)_2$D facilitates the production of serotonin in the brain and has a general protective and stimulating effect on brain and muscle tissue (12–15), whereas severe vitamin D deficiency causes myopathy (16). Additional evidence comes from studies with VDR knockout mice: these rodents showed abnormal muscle development, decreased muscle size and mass, altered grooming behavior, and increased anxiety (16).

A review of 37 previous RCTs examining the effects of vitamin D supplementation on depressive symptoms or physical functioning concluded that the study designs were too heterogeneous to draw conclusions (10). Supplementation dose, study duration, and participant inclusion criteria differed substantially between trials. Moreover, most of the previously conducted RCTs used a general population sample, whereas it can be expected that vitamin D supplementation is more effective and appropriate for persons with insufficient 25(OH)D concentrations and actual emotional and/or physical complaints. Furthermore, depressive symptoms and physical problems are highly interrelated and can reinforce each other (2, 3), which argues for a combined approach. For these reasons, the present RCT was designed.

The D-Vitaal trial investigated whether vitamin D supplementation could improve depressive symptoms, functional limitations, and physical performance in a high-risk older population with relatively low vitamin D status, clinically relevant depressive symptoms, and difficulties with physical functioning.

Methods

Study design

The D-Vitaal study is a randomized, double-blind, placebo-controlled trial designed to investigate the effects of vitamin D supplementation on depressive symptoms and physical functioning in older adults. The design and methods have been described elsewhere (10). The Medical Ethics Committee of the VU University Medical Center approved the study, and all participants provided written informed consent. The study is registered with the Netherlands Trial Register as NTR3845.

Setting and participants

The study was performed in Amsterdam and surroundings in the Netherlands from 2013 to 2016. Participants (n = 155) were community-dwelling persons aged 60–80 y recruited from the general population (81%) or through general practitioners (19%). Inclusion criteria were presence of depressive symptoms [as indicated by a Center of Epidemiological Studies–Depression scale (CES-D) score of ≥16 (17)], ≥1 functional limitation (e.g., difficulties with walking, climbing stairs, or dressing oneself), and a serum 25(OH)D concentration between 15 and 50 nmol/L in winter (October–March) or between 15 and 70 nmol/L in summer (April–September). These 25(OH)D cutoffs were based on the study by van Schoor et al. (18) that showed that the mean seasonal variation (winter–summer difference) of serum 25(OH)D in this age group is ∼20 nmol/L. This implies that persons with serum 25(OH)D concentrations of <70 nmol/L in summer will have inadequate vitamin D status (<50 nmol/L) in winter. Persons with a current major depressive disorder (MDD) diagnosis or life-threatening illness as well as persons currently using antidepressant medication, vitamin D supplements of >400 IU/d, or calcium supplements of >1000 mg/d were excluded.

Randomization and blinding

All participants who fulfilled the inclusion criteria were randomly allocated by an independent pharmacist in a 1:1 ratio in blocks of 4 to receive either vitamin D or placebo.

Participants were stratified by sex, and women were further stratified by age (60–70 y compared with 71–80 y), as we expected to include more women than men in the study (19–21). Participants, researchers, and research nurses were blinded to group allocation during the study. Group assignment was concealed until completion of the statistical analyses.

Intervention

The intervention consisted of a daily dose of 1200 IU vitamin D_3 (3 tablets of 400 IU cholecalciferol; Devaron) for 12 mo. The placebo group received identical tablets without vitamin D. All participants were allowed to take a (multi)vitamin D supplement with a maximum of 400 IU/d in addition to the study tablets. Furthermore, all participants were advised to use ≥3 dairy consumptions daily to ensure adequate calcium intake of ∼1000 mg/d. In case of <2 dairy consumptions per day, a calcium tablet of 500 mg/d was prescribed for the duration of the study.

Outcomes and follow-up

Primary outcomes.

Primary outcomes of the D-Vitaal study were depressive symptoms, functional limitations, and physical performance.

Depressive symptoms were assessed using the CES-D scale (17). This scale consists of 20 items and ranges from 0 to 60, with a higher score indicating more depressive symptoms. A score of ≥16 is indicative of clinically relevant depressive symptoms. This

outcome was defined as the difference in the 12-mo course of the depressive symptoms score between the 2 treatment groups.

Functional limitations were assessed using the Longitudinal Aging Study Amsterdam (LASA) Functional Limitations questionnaire (22). The participants were asked about their ability and degree of difficulty to perform the following functions of daily life: climbing stairs, cutting toenails, walking 5 min outdoors without resting, rising from a chair, dressing/undressing oneself, and using own or public transport. Two scores can be derived from this questionnaire: the number of functional limitations (score 0–6) and the severity of functional limitations (score 0–24). A higher score represents more functional limitations or more severe functional limitations, respectively. These outcomes were defined as the difference in the 12-mo course of the functional limitation scores between the 2 treatment groups.

Physical performance was assessed using a modified version of the Short Physical Performance Battery (SPPB) (9, 23). The SPPB includes a walking test, a repeated chair stand test, and a balance test. Participants could score 0–4 points on each test. Total scores range from 0 to 12, with higher scores representing better performance. This outcome was defined as the difference in the 12-mo course of the physical performance score between the 2 treatment groups.

Secondary outcomes.

Secondary outcomes included incidence of MDD, anxiety symptoms, cognitive function, health-related quality of life (HR-QoL), functional mobility, and muscle strength. In addition, we analyzed depressive symptoms and the number of functional limitations dichotomously.

The presence of MDD was assessed using the depression section of the Composite International Diagnostic Interview [version 2.1 (24)], which was administered only for CES-D scores of ≥16. Anxiety was assessed using the Beck Anxiety Inventory (BAI) (25). Cognitive function (i.e., information processing speed and executive functioning) was assessed using the Stroop Color-Word Test (26). HR-QoL was assessed using the EuroQol-5 Dimensions (EQ-5D) (27) and the Short Form–36 Health Survey (SF-36) (28). The timed up-and-go (TUG) test (29) was assessed to test functional mobility. Muscle strength was measured with a handgrip strength test using a strain-gauged dynamometer (Takei TKK 5401; Takei Scientific Instruments). Finally, in addition to the continuous primary analyses, depressive symptoms and number of functional limitations were analyzed dichotomously, with a CES-D cutoff of 16 (presence compared with absence of clinically relevant depressive symptoms) and a functional limitations cutoff of 1 (0 compared with ≥1 functional limitation).

Serum 25(OH)D measurements.

Serum 25(OH)D concentrations were measured at screening (baseline sample) and after 6 mo. Blood samples were drawn in the morning by a trained research nurse. Measurements were carried out using a well-standardized liquid chromatography followed by tandem mass spectrometry method (30, 31). Serum 25(OH)D concentrations at baseline were determined immediately after blood draw, whereas the 6-mo samples were measured all at once at the end of the study to ensure blinding. The 6-mo samples were stored at −80°C, with storage times until determination ranging from 6 to 27 mo.

Compliance.

Compliance was assessed by tablet count after 6 and 12 mo. A participant was considered compliant if ≥80% of the tablets had been taken during the 12 mo of follow-up. In addition, compliance of the participants in the intervention group was indicated by their serum 25(OH)D concentrations after 6 mo of supplementation. If these concentrations had increased by <10 nmol/L compared with baseline, and their 25(OH)D concentration at 6 mo was <75 nmol/L, participants were also considered noncompliant. During the study, compliance was stimulated by contacting the participants at 2 wk, 3 mo, and 9 mo by telephone and by reminding them during follow-up visits.

Adverse events.

Adverse events (AEs) were registered by telephone or face-to-face contact after 2 wk and after 3, 6, 9, and 12 mo. If necessary, the course of the AE was followed up by telephone.

Baseline characteristics and covariables.

Baseline characteristics included age, sex, season, marital status, educational level, smoking (yes/no), alcohol use [categories according to the Garretsen index (32)], BMI, waist and calf circumference, blood pressure and pulse rate, physical activity, chronic diseases, medication and supplement use, number of previous depressive episodes, use of psychological counseling, and predictors of vitamin D (sunlight exposure, skin pigmentation, fatty fish consumption).

Statistical analyses

Baseline characteristics were compared between the treatment groups with Pearson χ^2 tests (dichotomous or categorical variables) or Mann-Whitney tests (skewed continuous variables). Participants who dropped out were compared with participants who completed the study with respect to age, sex, serum 25(OH)D, and the primary outcome variables. These differences were tested with Mann-Whitney or Pearson χ^2 tests.

Differences between treatment groups in the total number of AEs were tested using a Mann-Whitney test, whereas group differences with regard to categories of AEs were tested with Pearson χ^2 tests.

Alcohol consumption was dichotomized into no/mild/moderate compared with (very) excessive alcohol use because the treatment groups differed in the latter category.

To assess the effects of the intervention, linear mixed-model analyses were conducted with the continuous primary and secondary outcome scores at 6 and 12 mo as a longitudinal outcome variable, treatment group as a fixed independent variable, and the baseline value of the outcome as a fixed covariate (model 1). In an additional model (model 2), we adjusted for any potential confounding variable that differed ($P < 0.10$) between treatment groups at baseline. We used an unstructured covariance structure and added a random intercept to the models to adjust for the dependency of the measures at 6 and 12 mo.

If the distribution of an outcome variable was skewed, a natural logarithmic (ln) transformation was performed. If this improved the distribution, analyses were conducted with the transformed variable. To interpret the results of the analyses with logarithmically transformed outcome variables, the resulting *B* values and CIs were transformed back. This back-transformation changes the *B* value into a ratio, here representing the difference between the intervention and placebo groups. For example, a ratio of 1.05 should be interpreted as a 5% higher outcome score in the intervention group compared with the placebo group.

Potential effect modification of age (continuous), sex, and baseline serum 25(OH)D concentrations (dichotomous, cutoffs of 50 and 30 nmol/L) was examined in the crude models by adding an interaction term (treatment × potential effect modifier). A time interaction term (treatment group × time point) was added to the crude models to investigate potential differences in effects between 6 and 12 mo of follow-up. If an interaction term had a *P* value of <0.10, stratified analyses were conducted. As the study was not powered for stratified analyses, we emphasize that these analyses are mainly exploratory.

Secondary dichotomous effect analyses for the CES-D score and number of functional limitations were conducted with general estimating equation analyses with an exchangeable correlation structure. Models and effect modification methods were similar to the continuous linear mixed-model analyses.

In preplanned sensitivity analyses, we examined whether change in serum 25(OH)D was associated with parallel change in the primary outcomes, irrespective of treatment group. For these analyses, change scores were created for 25(OH)D and the primary outcomes by calculating the difference between the values at baseline and 6 mo. Subsequently, multiple linear regression analyses were conducted with the change scores of the primary outcomes as dependent variables, change in serum 25(OH)D as the independent variable, and the baseline values of the independent and outcome variables as covariates. In a second model, we also adjusted for age, sex, season, marital status (CES-D analyses only), education level, alcohol use, smoking status, physical activity, and number of chronic diseases.

The intention-to-treat (ITT) analyses included all participants with ≥1 follow-up measurement. In the per-protocol effect analyses, we excluded participants who were not compliant according to the tablet count or otherwise not compliant with the study protocol. All results are ITT results unless otherwise stated. A double-sided *P* value of <0.05 was regarded as statistically significant. IBM SPSS Statistics version 22 (SPSS, Inc.) was used to perform all data analyses.

Power calculation

The statistical power analysis has been described in detail elsewhere (10). In short, the power calculation was based on the primary outcomes of depressive symptoms, functional limitations, and physical performance. To calculate the number of participants needed, a power of 80%, a 2-sided α of 0.05, and an intraclass correlation coefficient of 0.70 between baseline and follow-up measures were assumed. Based on a study with similar sample characteristics (33), ≥40 participants per group would be needed to detect a change of 0.5 SD (2.5 points) on the CES-D. For the number of functional limitations, we would need ≥28 participants per group to detect a meaningful change of 1 point, assuming a SD of 1.7. Regarding the severity of functional limitations, ≥48 participants per group would be needed to detect a change of 2 points, assuming a SD of 4.5. For physical performance, 22 persons per group would be needed to detect a meaningful change of 1 point on the SPPB, assuming a SD of 1.5. Taking into account an expected dropout of ∼25% and uncertainty of the 25(OH)D assay, ≥70 persons per group would be needed, adding up to ≥140 participants.

Results

Participant characteristics

Figure 1 displays the participant flow of the D-Vitaal study. We included 155 participants: 77 in the intervention group and 78 in the placebo group.

Baseline characteristics of the participants are presented in **Table 1**. The placebo group contained more heavy drinkers and current smokers than the intervention group. Participants in the intervention and placebo groups were not different regarding predictors of vitamin D status, use of vitamin D supplements, or other baseline characteristics (data partly shown in Table 1).

At baseline, 9 participants (5.8%) made use of any form of psychological counseling: 5 in the intervention group and 4 in the placebo group. Twenty-six participants (16.8%) started with any form of psychological counseling during the study: 12 in the intervention group and 14 in the placebo group (*P* for group difference = 0.69). Furthermore, 5 participants (3.2%, 3 in the intervention group and 2 in the placebo group) started with antidepressant medication during the study.

Forty-four participants (18 in the intervention group and 26 in the placebo group, *P* for group difference = 0.17) received a 500-mg/d calcium supplement in addition to the study tablets because they did not take ≥2 dairy consumptions per day [procedure as described in the study protocol (10)].

Ten participants dropped out during the study: 3 in the intervention group and 7 in the placebo group. Dropouts did not differ significantly from participants who completed the study with respect to age, sex, depressive symptoms, functional limitations, or physical performance (all $P > 0.05$), but participants who dropped out more often had serum 25(OH)D concentrations <30 nmol/L ($P = 0.034$).

In total, only 151 of the 155 initially randomly assigned participants could be included in the ITT analyses. Four participants (2 in both groups) had to be excluded because of insufficient data due to dropout shortly after the start of the study. Therefore, we refer to these analyses as modified ITT analyses, as not all initially randomly assigned participants could be included.

Compliance and serum 25(OH)D.

The average compliance according to tablet counts was 89.7%: 139 of 155 participants had a tablet intake of ≥80% throughout the study year, similar in both groups (*P* for group difference = 0.30). Furthermore, 4 participants in the intervention group had a <10-nmol/L increase in serum 25(OH)D in addition to a serum 25(OH)D concentration <75 nmol/L at 6 mo, which brings the total compliance to 87.1%.

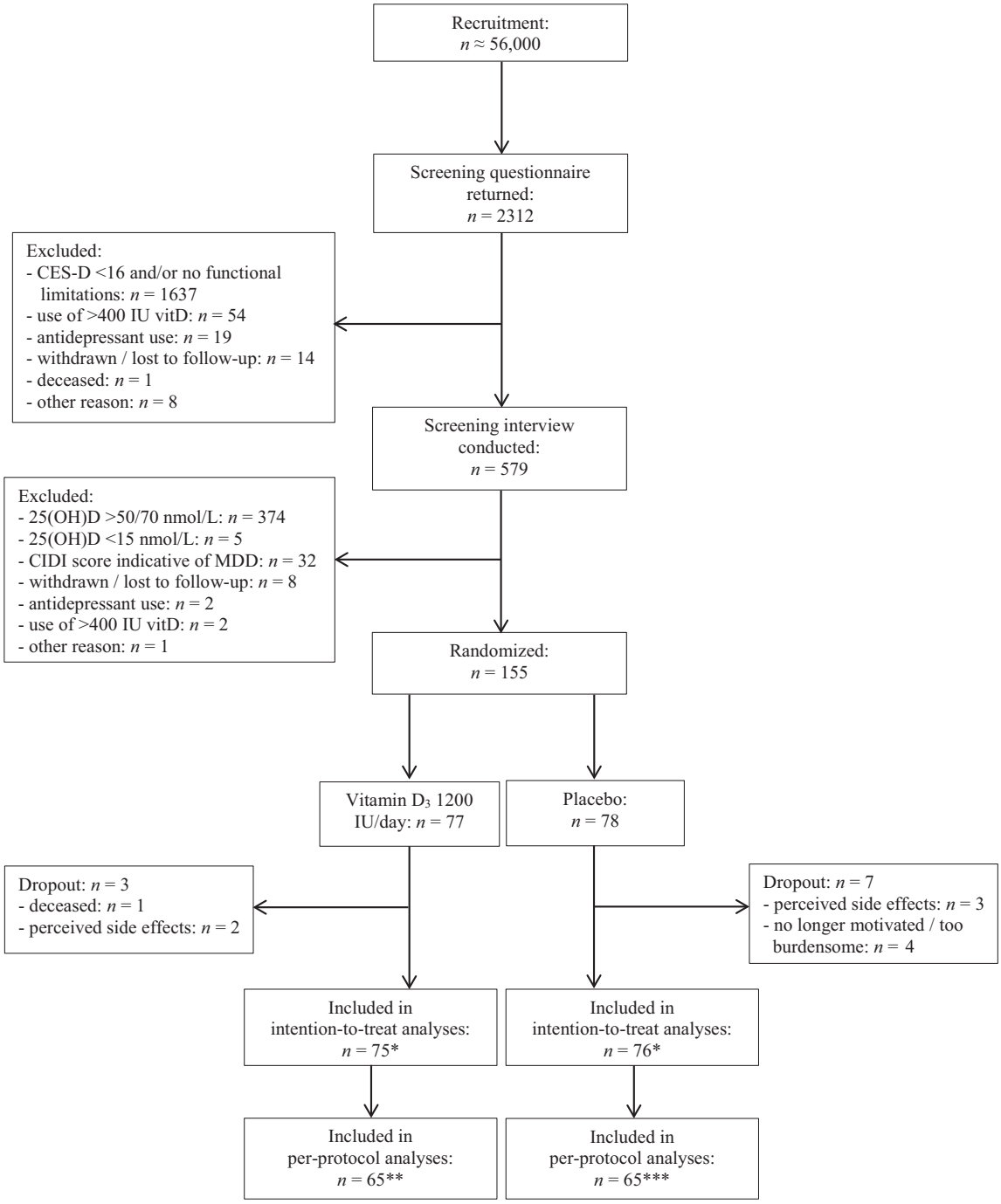

FIGURE 1 Recruitment, selection, randomization, and follow-up of participants in the D-Vitaal study. *$n = 2$ excluded from the intention-to-treat analyses due to insufficient data. **In the CES-D, BAI, SF-36 MCS, and EQ-5D analyses, an additional $n = 2$ were excluded completely, and the 12-mo measurements were excluded for another $n = 2$. ***In the CES-D, BAI, SF-36 MCS, and EQ-5D analyses, an additional $n = 1$ was excluded completely, and the 12-mo measurements were excluded for another $n = 3$ in all per-protocol analyses. BAI, Beck Anxiety Inventory; CES-D, Center of Epidemiological Studies–Depression scale; CIDI, Composite International Diagnostic Interview; EQ-5D, EuroQol-5 Dimensions; MDD, major depressive disorder; SF-36 MCS, Short Form–36 Health Survey Mental Component Summary; vitD, vitamin D; 25(OH)D, 25-hydroxyvitamin D.

In the intervention group, the mean ± SD serum 25(OH)D concentration after 6 mo of intervention was 85 ± 16 nmol/L compared with 43 ± 18 nmol/L in the placebo group (P for group difference < 0.001). The mean ± SD difference in 25(OH)D concentration after 6 mo compared with baseline was 40 ± 23 nmol/L for the intervention group compared with −2 ± 20 nmol/L for the placebo group. After 6 mo, all participants in the intervention group had reached serum 25(OH)D concentrations >50 nmol/L; 74.7% ($n = 56$) had reached ≥75 nmol/L, and 29.3% ($n = 22$) had reached ≥90 nmol/L. In the placebo group, 35.1% ($n = 26$) had a serum 25(OH)D concentration >50 nmol/L after 6 mo, 5.4% ($n = 4$) had reached ≥75 nmol/L, and 25.7% ($n = 19$) had a serum 25(OH)D concentration <30 nmol/L after 6 mo.

TABLE 1 Baseline characteristics of the D-Vitaal participants[1]

Characteristic	Intervention group ($n = 77$)	Placebo group ($n = 78$)
Serum 25(OH)D,[2] nmol/L	46 [32.5–57]	44 [36–55.25]
Baseline 25(OH)D <50 nmol/L[3]	47 (61.0)	52 (66.7)
Baseline 25(OH)D <30 nmol/L[3]	12 (15.6)	13 (16.7)
Age[2]	67.8 [65.4–71.7]	67.3 [63.4–72.0]
Women[3]	45 (58.4)	44 (56.4)
Season of baseline blood collection[3]		
Winter	33 (42.9)	30 (38.5)
Summer	44 (57.1)	48 (61.5)
Marital status[3]		
Never married/divorced	13 (16.9)	20 (26.0)
Married/living together/registered partner	49 (63.6)	46 (59.7)
Widowed	15 (19.5)	11 (14.3)
Education level[3,4]		
Low	22 (29.3)	21 (26.9)
Intermediate	36 (48.0)	34 (43.6)
High	17 (22.7)	23 (29.5)
Alcohol consumption[3,5#]		
None	17 (22.1)	12 (15.4)
Light	36 (46.8)	33 (42.3)
Moderate	21 (27.3)	20 (25.6)
(Very) excessive	3 (3.9)	13 (16.7)
Smoking[3*]		
No	70 (90.9)	59 (75.6)
Yes	7 (9.1)	19 (24.4)
BMI,[2] kg/m^2	27.1 [25.1–31.0]	26.9 [23.9–30.5]
Physical activity,[2] kcal/d	509 [332–802]	494 [271–791]
Number of chronic diseases[2]	2 [1–2]	1 [1–2]
Number of medications[2]	4 [2–6]	4 [2–6]
Former depression[3]	34 (44.7)	34 (43.6)
Anxiety (BAI)[2]	10 [5–18]	11 [6–18.75]
Stroop test (interference score)[2]	17.5 [12–23]	18.5 [14–25.5]
Timed up-and-go test[2]	7 [6–8.75]	7 [6–8]
Handgrip strength[2]	27.1 [21.8–38.1]	26.1 [21.9–37.9]
SF-36[2]		
Physical functioning subscale	70 [50–85]	70 [45–85]
Physical component summary score	46.4 [40.8–52.1]	46.0 [42.2–49.1]
Mental component summary score	39.6 [33.3–43.8]	37.3 [33.6–41.3]
EQ-5D[2]		
Index score	0.72 [0.65–0.84]	0.78 [0.69–0.84]
Visual analog scale	70 [50–80]	67 [50–75]
CES-D score[2]	22 [18–26.75]	21 [19–27]
Functional limitations[2]		
Number	2 [0.25–4]	1.5 [0–3.25]
Severity	2 [0.25–4.75]	2 [0–5]
Physical performance (SPPB)[2]	8 [6–10]	8.5 [6.75–11.0]

[1] Values are displayed as n (%) or as median [IQR]. $^{\#}P < 0.10$. $^{*}P < 0.05$. BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiological Studies–Depression scale; EQ-5D, EuroQoL-5 Dimensions; SF-36, Short Form–36 Health Survey; SPPB, Short Physical Performance Battery; 25(OH)D, 25-hydroxyvitamin D.

[2] Differences between treatment groups tested with Mann-Whitney test.

[3] Differences between treatment groups tested with Pearson χ^2 test.

[4] Education level categories: low (less than elementary, elementary, or lower vocational education), intermediate (general intermediate, intermediate vocational, or general secondary education), or high (higher vocational, college, or university education).

[5] Dichotomous analysis of alcohol use [no/mild/moderate compared with (very) excessive drinking]: $P < 0.01$.

AEs.

One participant in the intervention group died during the study. No statistically significant differences were observed between treatment groups with regard to the total number of AEs ($P = 0.24$) or categories of AEs (all $P > 0.05$, **Supplemental Table 1**).

Primary outcomes

As can be seen in **Table 2** and **Figure 2**, depressive symptoms and physical performance did not significantly differ between the 2 treatment groups over 12 mo. All interaction terms for these 2 outcomes were not significant ($P > 0.10$).

TABLE 2 Effect analyses of 12 mo of vitamin D supplementation compared with placebo on the primary and secondary outcomes (modified ITT)[1]

		Crude model[2]			Adjusted model[3]		
Characteristic	*n*	*B*/ratio	95% CI	*P*	*B*/ratio	95% CI	*P*
Primary outcomes		*B*			*B*		
Depressive symptoms (CES-D)	150	−0.25	−2.37, 1.87	0.82	−0.14	−2.36, 2.08	0.90
Functional limitations							
Number	150	−0.12	−0.42, 0.18	0.42	−0.11	−0.42, 0.20	0.48
Baseline 25(OH)D <50 nmol/L	*94*	*0.15*	*−0.25, 0.54*	*0.46*	*0.22*	*−0.20, 0.63*	*0.31*
Baseline 25(OH)D ≥50 nmol/L	*56*	*−0.62*	*−1.08, −0.17*	*0.008*	*−0.65*	*−1.11, −0.19*	*0.006*
Severity	150	0.02	−0.45, 0.50	0.93	−0.03	−0.52, 0.46	0.91
Baseline 25(OH)D <50 nmol/L	*94*	*0.35*	*−0.25, 0.96*	*0.25*	*0.30*	*−0.35, 0.94*	*0.36*
Baseline 25(OH)D ≥50 nmol/L	*56*	*−0.61*	*−1.39, 0.18*	*0.13*	*−0.64*	*−1.44, 0.16*	*0.12*
Physical performance (SPPB)	151	−0.05	−0.63, 0.54	0.88	−0.20	−0.79, 0.38	0.49
Secondary outcomes							
Health-related quality of life		*B*			*B*		
EQ-5D index score	150	−0.02	−0.07, 0.02	0.35	−0.02	−0.06, 0.03	0.52
Men	*64*	*0.03*	*−0.03, 0.10*	*0.31*	*0.03*	*−0.04, 0.11*	*0.34*
Women	*86*	*−0.06*	*−0.12, −0.00*	*0.046*	*−0.05*	*−0.11, 0.01*	*0.11*
EQ-5D visual analog scale	149	−3.14	−6.99, 0.72	0.11	−3.31	−7.32, 0.70	0.11
SF-36 Mental Component	148	−0.31	−2.01, 1.39	0.72	−0.22	−1.97, 1.54	0.81
SF-36 Physical Component	148	−0.26	−1.67, 1.14	0.71	−0.22	−1.67, 1.23	0.77
SF-36 Physical functioning subscale	140	0.32	−3.79, 4.43	0.88	0.27	−3.94, 4.48	0.90
Handgrip strength	150	−0.56	−1.66, 0.53	0.31	−0.65	−1.80, 0.50	0.27
		Ratio			*Ratio*		
Anxiety symptoms (BAI)[4]	147	1.05	0.86, 1.27	0.65	1.03	0.84, 1.26	0.79
Cognitive function (Stroop test)[4]	146	0.98	0.86, 1.13	0.83	0.97	0.84, 1.12	0.67
Timed up-and-go test[4]	148	1.02	0.95, 1.08	0.63	1.03	0.97, 1.10	0.32
Younger-old group (60–70 y)	*100*	*1.00*	*0.93, 1.08*	*0.99*	*1.03*	*0.95, 1.11*	*0.47*
Older-old group (71–80 y)	*48*	*1.02*	*0.92, 1.13*	*0.66*	*1.03*	*0.92, 1.14*	*0.62*

[1]Linear mixed-model analyses. Explorative stratified analyses are italicized. *P*s for interaction for the stratified analyses: number of functional limitations: $P = 0.020$; severity of functional limitations: $P = 0.084$; EQ-5D index score: $P = 0.041$; timed up-and-go test: $P = 0.087$. BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiological Studies–Depression scale; EQ-5D, EuroQoL-5 Dimensions; ITT, intention to treat; SF-36, Short Form–36 Health Survey; SPPB, Short Physical Performance Battery.

[2]Adjusted for the baseline value of the outcome variable.

[3]Additionally adjusted for alcohol use and smoking.

[4]Analyzed with ln-transformed outcome variable, the *B*s and 95% CIs were transformed back and should be interpreted as ratios, here representing the difference between the intervention and placebo groups. For example, a ratio of 1.05 should be interpreted as a 5% higher outcome score in the intervention group compared with the placebo group.

For both the number and severity of functional limitations, the interaction term of serum 25(OH)D (cutoff of 50 nmol/L) with treatment group was significant (P for interaction = 0.020 and 0.084, respectively), so the analyses for these outcomes were stratified by baseline 25(OH)D concentration, with a cutoff of 50 nmol/L. In the higher 25(OH)D group (≥50 nmol/L at baseline), the intervention group experienced fewer functional limitations compared with the placebo group over 12 mo, but the difference in the severity of functional limitations between the groups was not statistically significant. In the low 25(OH)D group (<50 nmol/L at baseline), both the number and severity of functional limitations did not differ significantly between the treatment groups (Table 2).

Secondary outcomes

Five participants (3.4%) developed MDD according to the Composite International Diagnostic Interview criteria in the course of the study period: 3 in the intervention group and 2 in the placebo group. Because of these low numbers, no further analyses were conducted.

In the dichotomous CES-D analyses, the time interaction term was significant (P for interaction = 0.072), indicating that the effect of the intervention at 6 mo was different from the effect at 12 mo. At 6 mo, more participants in the intervention group scored below the cutoff (no clinically relevant depressive symptoms) compared with the placebo group (55.6% compared with 44.4%, P in adjusted model = 0.09), indicating that the intervention group tended to experience fewer depressive symptoms. However, at 12 mo, this difference was no longer evident (48.8% compared with 51.3%, P in adjusted model = 0.63). The dichotomous analyses for the number of functional limitations yielded similar results as the continuous analyses: the P for interaction with baseline serum 25(OH)D was 0.056, so stratified analyses were performed. In the group with serum 25(OH)D concentrations ≥50 nmol/L, the intervention group more often had no functional limitations compared with the placebo group (OR in adjusted model = 0.21; 95% CI: 0.05, 0.88; $P = 0.032$) over 12 mo, whereas there was no significant difference between the treatment groups in the <50-nmol/L group (OR in adjusted model = 1.92; 95% CI: 0.46, 8.04; $P = 0.37$).

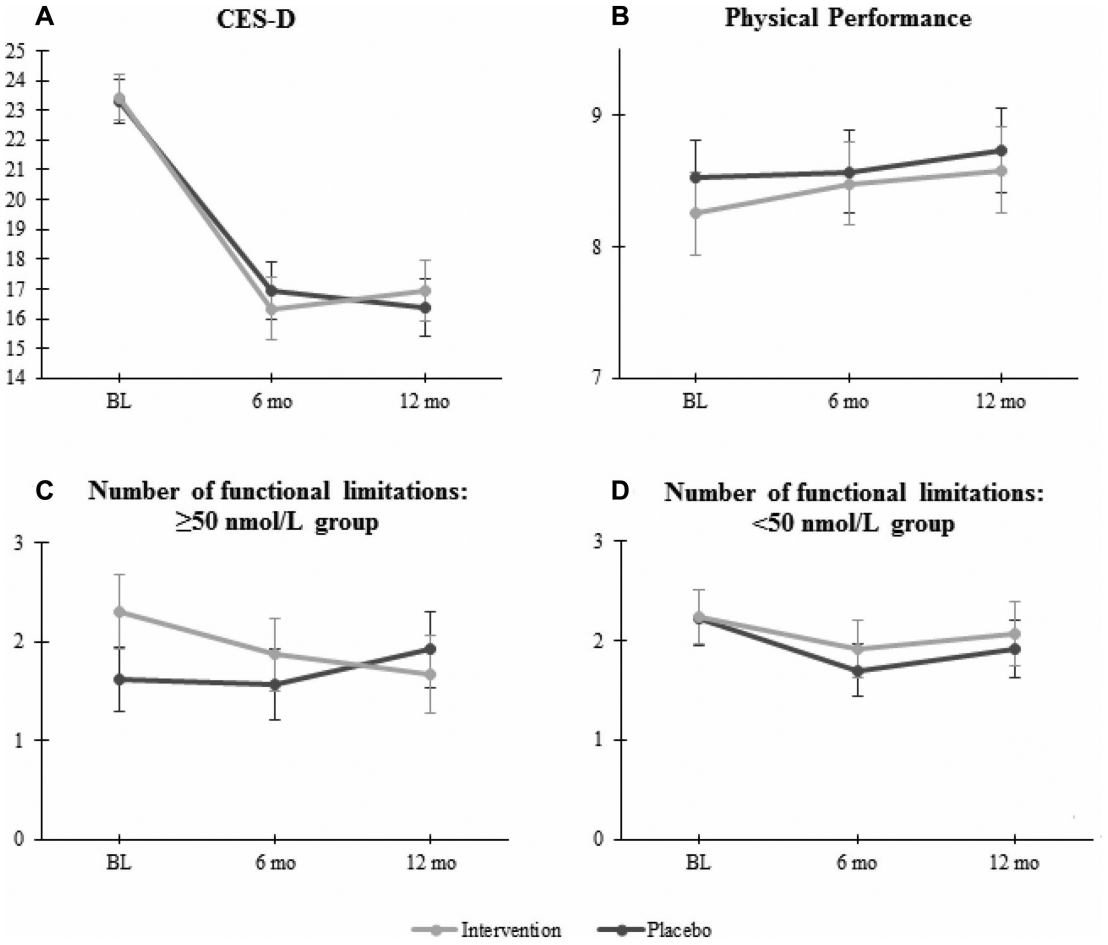

FIGURE 2 Mean scores of the primary outcome variables over time for the intervention and placebo groups. The error bars represent SEMs. *n* per group: (A) intervention: $n = 75$, placebo: $n = 75$; (B) intervention: $n = 75$, placebo: $n = 76$; (C) intervention: $n = 30$, placebo: $n = 26$; (D) intervention: $n = 44$, placebo: $n = 50$. *P* for interaction for the stratified analyses of number of functional limitations: $P = 0.020$. BL, baseline; CES-D, Center of Epidemiological Studies–Depression scale.

The analyses of the BAI anxiety questionnaire, Stroop test, and TUG test were conducted with ln-transformed scores, as their original distributions were skewed to the right. Significant effect modifiers included sex for the EQ-5D index score analysis (*P* for interaction = 0.041) and age in the TUG test analysis (*P* for interaction = 0.087). Therefore, the analyses of the EQ-5D index score were stratified for sex, and the TUG test analyses were stratified for age (60–69 compared with 70–80 y).

As Table 2 shows, the treatment groups did not significantly differ with regard to anxiety symptoms, cognitive functioning, the TUG test, handgrip strength, the SF-36 HR-QoL measures, and the EQ-5D Visual Analog Scale score over 12 mo (all $P > 0.10$). Only the EQ-5D index score showed a significantly lower score in women in the intervention group compared with women in the placebo group, but this effect disappeared in the adjusted analyses (Table 2).

Per-protocol analyses

Two data sets were created for the per-protocol analyses. In the first per-protocol data set, 21 participants were excluded completely for the following reasons: not compliant according to tablet count ($n = 16$), <10-nmol/L increase of serum 25(OH)D after 6 mo while being in the intervention group and having a serum 25(OH)D <75 nmol/L after 6 mo ($n = 4$), or otherwise not compliant with the study protocol ($n = 1$). For another 3 participants, only the 12-mo measurements were excluded due to noncompliance with the study protocol between 6 and 12 mo. This first data set was used to analyze all physical outcomes and the Stroop test. The second data set was created for the per-protocol analyses of the CES-D, BAI, SF-36 Mental Component Summary, and EQ-5D. This second data set was similar to the first data set, but an additional 3 participants were excluded due to antidepressant medication use ($n = 1$) or baseline CES-D scores below the inclusion cutoff (15 and 14, respectively, $n = 2$). Furthermore, the 12-mo measurements of another 2 participants were excluded due to antidepressant medication use between 6 and 12 mo in this second data set (the remaining 2 of 5 participants who started using antidepressant medication during the study were already excluded due to noncompliance for other reasons) (Figure 1).

All per-protocol analyses yielded results similar to the modified ITT analyses, although the effect of the supplementation on the number of functional limitations in the 25(OH)D ≥50-nmol/L

group was somewhat attenuated (crude model: $B = -0.51$, 95% CI: −0.98, −0.03, $P = 0.036$; adjusted model: $B = -0.53$, 95% CI: −1.02, −0.03, $P = 0.037$).

Additional analyses

Six-month change in serum 25(OH)D, independent of group assignment, was not significantly associated with parallel change in the CES-D score (B in adjusted model: −0.01, SE: 0.03, $P = 0.73$), functional limitations (number: B in adjusted model: −0.001, SE: 0.003, $P = 0.85$; severity: B in adjusted model: −0.004, SE: 0.01, $P = 0.51$), or physical performance (B in adjusted model: −0.01, SE: 0.01, $P = 0.32$).

Discussion

The D-Vitaal study investigated whether vitamin D_3 supplementation of 1200 IU/d for 12 mo would improve depressive symptoms, functional limitations, and physical performance in older persons with relatively low vitamin D status, clinically relevant depressive symptoms, and problems with physical functioning. The supplementation increased serum 25(OH)D concentrations in the intervention group to a mean of 85 nmol/L after 6 mo, whereas the placebo group remained stable at a mean of 43 nmol/L. However, the intervention had no significant effect on depressive symptoms, physical performance, the severity of functional limitations, or any of the secondary outcomes of the study (anxiety symptoms, cognitive functioning, mobility, grip strength, HR-QoL). Vitamin D supplementation had a small positive effect on the number of functional limitations in participants with serum 25(OH)D concentrations ≥50 nmol/L at baseline.

Similar to our study, several other RCTs did not observe an effect of vitamin D on depressive symptoms either (34–36). In a recent trial, Jorde and Kubiak (37) compared 4 mo of 20,000 IU/wk vitamin D with placebo in 408 participants and found no effect of the supplementation on the Beck Depression Inventory. Baseline vitamin D status was <42 nmol/L, but relatively few participants had depressive symptoms. Moreover, the authors attributed positive findings from their previous RCTs on this topic (38, 39) to chance. In contrast, 3 smaller trials that included persons with both low vitamin D status and MDD did demonstrate a reduction in depression after vitamin D supplementation (40–42). These 3 studies included participants with a depression diagnosis, as opposed to subthreshold depression in our trial, which may explain the discrepancy in results.

Regarding the effect of vitamin D supplementation on physical functioning, recent RCTs reported no effect on gait speed, balance, physical performance, or muscle strength either (43–45), even though these studies included participants with lower vitamin D status and impaired physical functioning. On the contrary, a study with postmenopausal women aged 50–65 y with mean baseline 25(OH)D concentrations of 40 nmol/L and a history of falling showed that 1000 IU/d for 9 mo had a positive effect on lower extremity muscle strength and balance (46, 47). Possibly, these differences between trial results can be attributed to differences in measurement and sample characteristics.

There is a growing consensus that for many outcomes, including depression and physical functioning, supplementation with vitamin D is beneficial only in persons with low serum 25(OH)D concentrations (<50 nmol/L) (48–50). In an extensive review of trial data, Rejnmark et al. (51) evaluated the current evidence regarding the extraskeletal effects of vitamin D and noted that most studies were conducted with persons with replete 25(OH)D concentrations, which may explain the null findings of many trials. Nevertheless, the D-Vitaal study shows the absence of an effect of vitamin D supplementation in a high-risk sample with relatively low vitamin D status.

The small but statistically significant positive effect of the intervention on the number of functional limitations in the group with baseline 25(OH)D concentrations ≥50 nmol/L was surprising. We expected an effect of the supplementation on the outcomes to be more pronounced in persons with the lowest baseline 25(OH)D concentrations. Furthermore, the ≥50-nmol/L group did not reach higher 25(OH)D concentrations after 6 mo compared with the <50-nmol/L group. We therefore believe that, besides not being clinically relevant (52), this effect is most likely a chance finding. Furthermore, our study was not specifically powered for stratified analyses, so these analyses were mainly exploratory.

Strengths of the D-Vitaal study include the double-blind, randomized, placebo-controlled design, with inclusion of persons hypothesized to optimally benefit from the supplementation: an older population with depressive symptoms, poor physical functioning, and relatively low vitamin D status. Dropout was relatively low (6.5%), and compliance was high (87%). To examine the effects of the intervention, we used longitudinal statistical techniques to make optimal use of the available data.

A potential limitation of the present study is the relatively small n of 155 persons, although this number was sufficient according to the power calculation (10). Nevertheless, considering the small effect sizes, it is doubtful that a larger sample size would have yielded different results. Another potential limitation is that we included participants with a maximum serum 25(OH)D concentration of 70 nmol/L in summer. In winter, the limit was set to 50 nmol/L. We checked for interaction effects with baseline 25(OH)D (cutoffs of 50 and 30 nmol/L), but the group with <30 nmol/L at baseline may have been too small to detect an interaction effect. It is possible that our inclusion criteria regarding serum 25(OH)D were too liberal. Potentially, a limit of <50 nmol/L in summer and <30 nmol/L in winter would yield different results, but this would also complicate recruitment considerably. As an additional explorative analysis, we tested whether analyses stratified at a baseline serum 25(OH)D of 30 nmol/L would show a different picture for the primary outcomes, even though the interaction effect was not statistically significant. However, all results were nonsignificant (data not shown), but due to the small n in the <30-nmol/L group, the validity of these results is uncertain.

Presence of MDD and use of antidepressant medication were exclusion criteria in our study; we included only persons with subthreshold depression (CES-D ≥16). Therefore, we may have included persons who had only short-lived symptoms at the time of inclusion and improved naturally over time. This could explain the drop in CES-D scores in both groups between baseline and 6 mo (Figure 2A). However, the mean CES-D score remained around 16 in both groups at 6 and 12 mo, demonstrating that a substantial proportion of participants had clinically relevant depressive symptoms throughout the study period.

Compared with other supplementation trials, our vitamin D dose of 1200 IU/d is relatively low. Nevertheless, participants in the intervention group were replete at 6 mo, with a mean 25(OH)D concentration of 85 nmol/L. As serum 25(OH)D concentrations tend to reach a plateau after a few months of supplementation (53), similar concentrations are assumed after 12 mo. Recent research indicates that higher doses are not more effective and can even be harmful, for instance, by increasing the number of falls or reducing muscle strength (50, 54, 55).

It is remarkable that observational studies have demonstrated rather consistent associations between vitamin D status and numerous health outcomes, whereas this is often not confirmed by trial evidence (56, 57). Therefore, it is more likely that vitamin D status is a marker for poor health or inflammation instead of a cause of disease (58).

At the moment, several large-scale, long-term RCTs are being conducted to examine the effects of vitamin D supplementation on multiple outcomes in older persons: the Vitamin D Assessment Study (ViDa) trial (n = 5110, 100,000 IU/mo for a median period of 3.3 y) (59), the VITamin D and OmegA-3 (VITAL) trial and its ancillary the VITamin D and OmegA-3 Trial–Depression Endpoint Prevention (VITAL–DEP) study (n = 25,874, 2000 IU/d for a mean period of 5 y) (60, 61), and the Vitamin D3–Omega3–Home Exercise –HeALTHy Ageing and Longevity Trial (DO-HEALTH) (n = 2152, 2000 IU/d for 3 y) (62). Although these trials use general population samples, the n is large enough to allow for subgroup analyses. The outcomes of these trials will shed more light on the complex relationship of vitamin D with depression and physical functioning. In addition, there may be some potential in the combination of antidepressants with vitamin D in the treatment of depression (63), although a recent report suggests that it can be challenging to conduct such an RCT (64).

The D-Vitaal recruitment phase was also challenging. We had to send out ~56,000 information brochures to include 155 participants, which underlines the difficulty of recruiting for this type of RCT in the general population. Most of the potential participants did not respond to our invitation, which might have been due to ineligibility or lack of interest to participate in an RCT. Including participants with even lower baseline serum 25(OH)D concentrations (<30 nmol/L) would be of great scientific interest but will be complicated to accomplish, both ethically and practically.

Based on the results of this study, supplementation with vitamin D for the prevention of depression and poor physical functioning cannot be recommended. However, it is important to continue research for effective and acceptable prevention strategies for these health problems in older persons.

In conclusion, this randomized placebo-controlled trial found no effect of 1200 IU/d vitamin D supplementation for 1 y on depressive symptoms or physical functioning in a high-risk population with relatively low vitamin D status.

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The authors' responsibilities were as follows—NMvS and PL: primarily designed the D-Vitaal study, and all other authors contributed to the design; PL: was the principal investigator; NMvS: was the trial coordinator; EJdK, NMvS, HWJvM, BWJHP, PJME, and PL: conducted the research; ACH: coordinated the serum 25(OH)D determinations; PMB: coordinated the issuing of the study tablets; MdH: assisted with the power analysis; EJdK: collected the data (together with the research assistants), performed the statistical analyses, and wrote the paper; and all authors read and approved the final manuscript. BWJHP has received research funding from Jansen Research and Boehringer Ingelheim outside the submitted work. All other authors have nothing to disclose.

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