Effects of Vitamin D in Physical Function: Results from the STURDY Trial

Online Supplement

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eTable 1. Characteristics of randomized participants at enrollment (full version).

	Primary Analysis Population (N=688)			4-Dose Analysis Population[b] (N=406)				
	Pooled Higher Doses[a] (N=349)	200 IU/d (N=339)	Those randomized to 1000 IU/d (N=212)	1000 IU/d (N=67)	2000 IU/d (N=67)	4000 IU/d (N=67)	200 IU/d (N=205)	All (N=688)
Age (years), mean ± SD	77.2 ± 5.4	77.2 ± 5.4	76.5 ± 5.3	76.4 ± 4.4	77.3 ± 4.6	79.1 ± 5.9	77.8 ± 5.6	77.2 ± 5.4
Male, no. (%)	190 (54.4%)	198 (58.4%)	110 (51.9%)	38 (56.7%)	38 (56.7%)	40 (59.7%)	117 (57.1%)	388 (56.4%)
Race, no. (%)[c]								
White	267 (77.2%)	276 (82.4%)	159 (75.7%)	49 (73.1%)	50 (75.8%)	56 (83.6%)	171 (83.4%)	543 (79.7%)
Black	69 (19.9%)	55 (16.4%)	44 (21.0%)	13 (19.4%)	15 (22.7%)	10 (14.9%)	32 (15.6%)	124 (18.2%)
Other	16 (4.6%)	7 (2.1%)	12 (5.7%)	5 (7.5%)	2 (3.0%)	1 (1.5%)	4 (2.0%)	23 (3.4%)
No. missing	3	4	2	0	1	0	0	7
Hispanic, Latino or Spanish ethnicity, no. (%)	5 (1.4%)	3 (0.9%)	3 (1.4%)	2 (3.0%)	1 (1.5%)	1 (1.5%)	2 (1.0%)	8 (1.2%)
No. missing	1	3	1	0	0	0	2	4
Serum 25(OH)D (ng/mL)								
10-19, no. (%)	100 (28.7%)	100 (29.5%)	53 (25.0%)	15 (22.4%)	25 (37.3%)	22 (32.8%)	69 (33.7%)	200 (29.1%)
20-29, no. (%)	249 (71.3%)	239 (70.5%)	159 (75.0%)	52 (77.6%)	42 (62.7%)	45 (67.2%)	136 (66.3%)	488 (70.9%)
Mean ± SD	22.1 ± 4.9	22.1 ± 5.3	22.6 ± 4.7	22.1 ± 4.1	21.0 ± 5.3	21.2 ± 4.9	21.5 ± 5.3	22.1 ± 5.1
Median (Q25, Q75)	23 (19, 26)	23 (18, 27)	23 (19.5, 26)	22 (20, 25)	22 (17, 25)	22 (17, 25)	23 (17, 26)	23 (19, 26)
Taking a vitamin D supplement, no. (%)	132 (37.8%)	124 (36.6%)	82 (38.7%)	27 (40.3%)	26 (38.8%)	21 (31.3%)	76 (37.1%)	256 (37.2%)
Median (Q25, Q75) daily dose (IU)	700 (400, 1000)	800 (414.5, 1000)	650 (400, 1000)	800 (400, 900)	800 (500, 1000)	571 (400, 800)	800 (414.5, 1000)	700 (400, 1000)
Low physical activity[d], no. (%)	43 (12.4%)	47 (13.9%)	27 (12.9%)	7 (10.6%)	7 (10.4%)	9 (13.4%)	39 (19.0%)	90 (13.1%)
No. missing	2	0	2	1	0	0	0	2
SPPB total score[e]								
0 to 8, no. (%)	138 (39.5%)	115 (33.9%)	80 (37.7%)	33 (49.3%)	29 (43.3%)	29 (43.3%)	72 (35.1%)	253 (36.8%)
9-12, no. (%)	211 (60.5%)	224 (66.1%)	132 (62.3%)	34 (50.7%)	38 (56.7%)	38 (56.7%)	133 (64.9%)	435 (63.2%)
Mean ± SD	8.6 ± 2.5	8.9 ± 2.3	8.8 ± 2.6	8.4 ± 2.5	8.2 ± 2.4	8.5 ± 2.5	8.7 ± 2.3	8.7 ± 2.4

	Primary Analysis Population (N=688)		Those randomized to 1000 IU/d (N=212)	4-Dose Analysis Population[b] (N=406)				All (N=688)
	Pooled Higher Doses[a] (N=349)	200 IU/d (N=339)		1000 IU/d (N=67)	2000 IU/d (N=67)	4000 IU/d (N=67)	200 IU/d (N=205)	
SPPB total balance stand[e] time (s)								
Mean ± SD	26.6 ± 6.2	26.9 ± 6.3	26.7 ± 6.6	26.9 ± 6.4	26.1 ± 6.0	27.0 ± 5.2	26.4 ± 6.8	26.8 ± 6.2
No. missing	0	1	0	0	0	0	1	1
SPPB gait speed (m/s)[e]								
< 0.6 m/s	46 (13.3%)	35 (10.4%)	24 (11.4%)	10 (15.2%)	11 (16.4%)	11 (16.4%)	21 (10.3%)	81 (11.8%)
≥ 0.6 m/s	301 (86.7%)	303 (89.6%)	186 (88.6%)	56 (84.8%)	56 (83.6%)	56 (83.6%)	183 (89.7%)	604 (88.2%)
Mean ± SD	0.84 ± 0.23	0.89 ± 0.23	0.85 ± 0.23	0.81 ± 0.24	0.80 ± 0.23	0.84 ± 0.23	0.88 ± 0.21	0.86 ± 0.24
No. missing	2	1	2	1	0	0	1	3
SPPB chair stand time (s)[e]								
Mean ± SD	15.7 ± 6.4	15.2 ± 5.0	14.7 ± 4.4	15.8 ± 4.2	17.2 ± 6.4	17.3 ± 10.5	15.7 ± 5.2	15.4 ± 5.7
No. missing	39	31	23	7	7	9	17	70
TUG time (s)[f]								
< 12 s	228 (66.1%)	251 (74.9%)	140 (67.0%)	44 (66.7%)	41 (61.2%)	44 (66.7%)	151 (74.4%)	479 (70.4%)
≥ 12 s	117 (33.9%)	84 (25.1%)	69 (33.0%)	22 (33.3%)	26 (38.8%)	22 (33.3%)	52 (25.6%)	201 (29.6%)
Mean ± SD	12.1 ± 5.9	11.1 ± 4.6	12.1 ± 6.6	12.6 ± 6.9	12.5 ± 5.2	11.9 ± 3.9	11.2 ± 3.9	11.6 ± 5.3
No. missing	4	4	3	1	0	1	2	8
6 minute walk[g]								
No. not starting walk	43	28	31	9	6	6	14	71
Those starting walk								
No.	306	311	181	58	61	61	191	617
Distance (m), mean ± SD	307 ± 89	322 ± 90	310 ± 81	305 ± 85	294 ± 87	308 ± 111	316 ± 88	315 ± 90
Those walking 6 minutes								
No. (% of those starting)	295 (96.4%)	300 (96.5%)	177 (97.8%)	55 (94.8%)	58 (95.1%)	57 (93.4%)	183 (95.8%)	595 (96.4%)
Distance (m), mean ± SD	313 ± 82	330 ± 81	313 ± 76	310 ± 77	298 ± 87	324 ± 94	325 ± 78	321 ± 82

	Primary Analysis Population (N=688)		Those randomized to 1000 IU/d (N=212)	4-Dose Analysis Population[b] (N=406)				
	Pooled Higher Doses[a] (N=349)	200 IU/d (N=339)		1000 IU/d (N=67)	2000 IU/d (N=67)	4000 IU/d (N=67)	200 IU/d (N=205)	All (N=688)
Grip strength (kg)[h]								
Females, no. in dose group	159	141	102	29	29	27	88	300
Mean ± SD	18.9 ± 5.8	18.1 ± 6.5	18.6 ± 6.0	19.2 ± 4.6	19.8 ± 5.5	19.0 ± 5.5	19.4 ± 5.8	18.5 ± 6.2
No. missing	7	3	7	1	0	0	3	10
Males, no. in dose group	190	198	110	38	38	40	117	388
Mean ± SD	29.2 ± 9.6	30.6 ± 9.0	27.9 ± 9.4	30.7 ± 8.8	31.8 ± 10.2	30.4 ± 9.3	30.9 ± 8.9	29.9 ± 9.3
No. missing	2	4	1	1	1	0	0	6

Note. IU/d = international units per day; SD = standard deviation; SPPB = Short Physical Performance Battery; TUG = Timed Up-and-Go test.

[a]Pooled Higher Doses denotes the combined 1000, 2000, and 4000 IU/d groups.

[b]The 4-dose analysis population includes all participants randomized prior to the first adaptation of the randomization probabilities.

[c]More than one race could be reported by a participant; race was self-reported.

[d]Physical activity level was considered low if <128 kcal/wk (males) or <90 kcal/wk (females).

[e]The Short Physical Performance Battery (SPPB) is a 3-part assessment of physical functioning: balance testing, timed 4-meter walk, and ability to stand up from a seated position in a chair; each part is scored 0 to 4 and the total SPPB score (range 0 to 12) is the sum of the 3 subscores. Higher scores indicate better physical function. The total balance stand time (range 0-30 seconds) combines the stand durations from the 3 balance tests. Gait speed was calculated as 4 meters divided by the duration of the walk in seconds. The chair stand test outcome is the time required to complete 5 chair stands and the test is terminated at 60 seconds if not completed by that time.

[f]The Timed Up-and-Go (TUG) test is a timed test of standing up from a chair, walking at normal pace for 3 meters, turning, returning to the chair, and sitting down; the test result is the time in seconds to complete all 5 parts. The test is terminated at 60 seconds if not completed by that time.

[g]The 6-minute walk is a test of endurance; the participant is instructed to walk at maximum pace for 6 minutes and the score is distance covered. Each site used a straight line course 10 meters in length; each end was marked with a cone which the participant had to walk around. Total distance walked was recorded for each participant who started the walk.

[h]Grip strength is the maximum of 3 tries with the dominant hand of a hand-held dynamometer; if the dominant hand could not be tested, results for the non-dominant hand were used.

eTable 2. Serum 25(OH)D level (ng/mL) over time by treatment group and use of a personal vitamin D supplement at enrollment.

		Enrollment	3 months	12 months	24 months
PHD	Abs level, mean ± SD	22.1 ± 4.9	36.4 ± 10.7	38.8 ± 12.0	39.7 ± 11.9
	Chg from BL, mean ± SD		14.3 ± 11.3	16.8 ± 12.3	18.0 ± 12.4
	No. in group	349	323	254	160
200 IU/d	Abs level, mean ± SD	22.1 ± 5.3	27.0 ± 5.8	27.5 ± 6.7	28.2 ± 6.7
	Chg from BL, mean ± SD		4.9 ± 5.7	5.5 ± 6.6	6.4 ± 6.9
	No. in group	339	314	261	168
PHD v. 200 IU/d	Diff betw means (95% CI)		9.4 (8.0, 10.8)	11.4 (9.6, 13.1)	11.6 (9.4, 13.7)
Not using a personal vitamin D supplement at enrollment					
PHD	Abs level, mean ± SD	20.9 ± 5.1	36.6 ± 10.5	39.9 ± 13.2	39.8 ± 11.9
	Chg from BL, mean ± SD		15.6 ± 11.4	19.0 ± 13.5	19.2 ± 12.3
	No. in group	217	199	158	101
200 IU/d	Abs level, mean ± SD	20.4 ± 5.4	26.1 ± 5.6	26.8 ± 7.0	27.4 ± 7.0
	Chg from BL, mean ± SD		5.7 ± 5.9	6.6 ± 7.1	7.5 ± 7.1
	No. in group	215	199	166	105
PHD v. 200 IU/d	Diff betw means (95% CI)		9.9 (8.1, 11.7)	12.4 (10.0, 14.7)	11.6 (8.9, 14.4)
Using a personal vitamin D supplement at enrollment					
PHD	Abs level, mean ± SD	24.0 ± 4.0	36.2 ± 11.0	36.9 ± 9.3	39.6 ± 12.1
	Chg from BL, mean ± SD		12.2 ± 10.9	13.3 ± 9.1	15.9 ± 12.4
	No. in group	132	124	96	59
200 IU/d	Abs level, mean ± SD	25.3 ± 3.2	28.5 ± 5.7	28.6 ± 5.8	29.5 ± 5.9
	Chg from BL, mean ± SD		3.4 ± 5.0	3.6 ± 5.1	4.5 ± 6.1
	No. in group	124	115	95	63
PHD v. 200 IU/d	Diff betw means (95% CI)		8.8 (6.6, 11.0)	9.8 (7.6, 11.9)	11.4 (7.9, 14.8)

Abbreviations: BL = baseline; CI = confidence interval; IU/d = international units per day; PHD = Pooled Higher Doses.
Note: Pooled Higher Doses denotes the combined 1000, 2000, and 4000 IU/d groups.

eTable 3. Change in 6-minute walk and grip strength since randomization in the primary analysis population.

	3 months		12 months		24 months		P, interaction[b]	
	Pooled Higher Doses[a]	200 IU/d	Pooled Higher Doses[a]	200 IU/d	Pooled Higher Doses[a]	200 IU/d	Unadj	Adj (significant if < 0.11)
6 minute walk distance (all who started the walk; m)[c]								
No. of participants in analysis	253	260	190	207	115	129		
BL, mean ± SD[d]	317 ± 82	330 ± 89	325 ± 84	332 ± 85	327 ± 82	346 ± 79		
Change (FU-BL), mean ± SD	6 ± 46	5 ± 48	-4 ± 56	-8 ± 54	-9 ± 67	-14 ± 49		
P, change within group[e]	0.05	0.12	0.32	0.04	0.15	0.002		
P, difference between groups[b]	0.66		0.27		0.72		0.75	0.91
6 minute walk distance (those who walked 6 min) (m)[c]								
No. of participants in analysis	243	245	180	194	110	127		
BL, mean ± SD[d]	322 ± 77	339 ± 80	331 ± 77	340 ± 77	333 ± 76	350 ± 73		
Change (FU-BL), mean ± SD	5 ± 45	6 ± 45	-4 ± 50	-4 ± 45	-8 ± 62	-14 ± 49		
P, change within group[e]	0.07	0.06	0.31	0.23	0.18	0.002		
P, difference between groups[b]	>0.99		0.42		0.62		0.82	0.91
Grip strength (kg), females[f]								
No. of participants in analysis	131	122	94	99	61	63		
BL, mean ± SD[d]	19.3 ± 5.7	18.6 ± 6.5	19.2 ± 5.7	19.3 ± 6.1	19.9 ± 5.4	20.0 ± 6.0		
Change (FU-BL), mean ± SD	-0.5 ± 4.1	-1.0 ± 5.3	-1.4 ± 4.3	-1.3 ± 5.0	-2.0 ± 5.0	-2.2 ± 5.3		
P, change within group[e]	0.13	0.03	0.002	0.008	0.002	0.002		
P, difference between groups[b]	0.54		0.57		0.77		0.72	0.91
Grip strength (kg), males[f]								
No. of participants in analysis	176	177	142	143	89	96		
BL, mean ± SD[d]	29.7 ± 9.5	30.9 ± 9.1	30.3 ± 9.7	31.3 ± 9.0	32.3 ± 9.3	31.9 ± 8.8		
Change (FU-BL), mean ± SD	-0.5 ± 6.2	-0.2 ± 5.2	-2.0 ± 6.9	-1.3 ± 7.0	-2.1 ± 5.7	-2.8 ± 4.8		
P, change within group[e]	0.33	0.65	0.001	0.03	0.001	<0.001		
P, difference between groups[b]	0.63		0.33		0.40		0.42	0.81

Note. BL = baseline; FU = follow-up; IU/d = international units per day; SD = standard deviation.

[a]Pooled Higher Doses denotes the combined 1000, 2000, and 4000 IU/d groups.

[b]A longitudinal mixed effects linear regression model with fixed effects including a single term for treatment, 3 time point terms, and 3 treatment-by-time interaction terms and a random intercept for participant was fit for each outcome; this model included all available measures of the outcome for all participants, including those with only a baseline measure. Each time-specific P value for difference between dose groups is derived from the corresponding treatment-by-time interaction term. The interaction P test for overall difference between groups in differential change from baseline is from a 3-degree of

freedom test of the combined 3 treatment-by-time interaction terms from the longitudinal model. The Benjamini-Hochberg procedure was used to control the false discovery rate to less than 1/9 (1 out of the maximum number of overall comparisons in each family of analyses (table or figure) comparing dose groups; an adjusted P value is statistically significant if <0.11.

[c]The 6-minute walk is a test of endurance; the participant is instructed to walk at maximum pace for 6 minutes and the score is distance covered. Each site used a straight line course 10 meters in length; each end was marked with a cone which the participant had to walk around. Total distance walked was recorded for each participant who started the walk.

[d]Baseline values are shown for those with a follow-up measure at the given time point.

[e]P values for time-specific change within group were derived from t-tests.

[f]Grip strength is the maximum of 3 tries with the dominant hand of a hand-held dynamometer; if the dominant hand could not be tested, results for the non-dominant hand were used.

eTable 4. Sensitivity analysis: Change in functional outcome measures since randomization in those randomized to 1000 IU/d versus those randomized to 200 IU/d.

	3 months		12 months		24 months		P, interaction[a]	
	1000 IU/d	200 IU/d	1000 IU/d	200 IU/d	1000 IU/d	200 IU/d	Unadj	Adj (significant if <0.11)
SPPB score[b]								
No. in analysis	196	314	135	260	58	171		
BL, mean ± SD[c]	8.8 ± 2.5	8.9 ± 2.3	8.9 ± 2.4	9.0 ± 2.2	8.6 ± 2.5	9.0 ± 2.2		
Chg (FU-BL), mean ± SD	-0.2 ± 1.6	0.0 ± 1.9	-0.3 ± 2.0	-0.2 ± 1.9	-0.5 ± 2.5	-0.8 ± 2.5		
P, chg within group[d]	0.12	0.88	0.05	0.06	0.15	<0.001		
P, difference between groups[a]	0.46		0.53		0.73		0.76	0.76
Total SPPB balance stand time (s)[b]								
No. in analysis	196	313	135	259	58	170		
BL, mean ± SD[c]	26.9 ± 6.3	26.9 ± 6.3	27.5 ± 5.4	27.3 ± 5.9	27.3 ± 6.6	26.7 ± 6.8		
Chg (FU-BL), mean ± SD	0.4 ± 5.5	0.1 ± 6.3	-0.7 ± 6.1	0.1 ± 6.0	-2.4 ± 7.7	-1.3 ± 9.0		
P, chg within group[d]	0.27	0.77	0.16	0.84	0.02	0.07		
P, difference between groups[a]	0.47		0.50		0.52		0.52	0.76
SPPB gait speed (m/s)[b]								
No. in analysis	194	309	131	258	55	162		
BL, mean ± SD[c]	0.85 ± 0.24	0.89 ± 0.23	0.88 ± 0.24	0.90 ± 0.24	0.85 ± 0.27	0.93 ± 0.23		
Chg (FU-BL), mean ± SD	-0.03 ± 0.17	-0.01 ± 0.18	-0.04 ± 0.18	-0.04 ± 0.20	-0.01 ± 0.17	-0.09 ± 0.21		
P, chg within group[d]	0.03	0.58	0.02	0.001	0.61	<0.001		
P, difference between groups[a]	0.27		0.80		0.07		0.09	0.45
SPPB chair stands time (s)[b]								
No. in analysis	167	276	109	219	43	128		
BL, mean ± SD[c]	14.5 ± 4.3	15.1 ± 4.9	14.8 ± 4.5	15.1 ± 4.6	15.2 ± 4.1	14.8 ± 4.2		
Chg (FU-BL), mean ± SD	0.0 ± 4.0	-0.2 ± 4.4	-0.9 ± 4.8	-0.3 ± 4.6	-1.6 ± 4.3	-0.6 ± 3.6		
P, chg within group[d]	0.93	0.38	0.07	0.30	0.02	0.05		
P, difference between groups[a]	0.73		0.42		0.68		0.72	0.76
TUG time (s)[e]								
No. in analysis	191	305	128	255	52	159		
BL, mean ± SD[c]	11.9 ± 6.7	11.0 ± 4.6	11.1 ± 5.1	10.8 ± 3.5	11.3 ± 4.7	10.4 ± 3.0		
Chg (FU-BL), mean ± SD	-0.2 ± 2.7	0.3 ± 4.0	0.3 ± 2.5	0.5 ± 2.3	0.4 ± 2.5	1.1 ± 2.5		
P, chg within group[d]	0.29	0.15	0.12	0.001	0.28	<0.001		
P, difference between groups[a]	0.04		0.24		0.07		0.13	0.45

	3 months		12 months		24 months		P, interaction[a]	
	1000 IU/d	200 IU/d	1000 IU/d	200 IU/d	1000 IU/d	200 IU/d	Unadj	Adj (significant if <0.11)
6 minute walk distance (all who started the walk; m)[f]								
No. in analysis	146	260	101	207	40	129		
BL, mean ± SD[c]	319 ± 73	330 ± 89	329 ± 73	332 ± 85	325 ± 81	346 ± 79		
Chg (FU-BL), mean ± SD	7 ± 47	5 ± 48	0 ± 60	-8 ± 54	9 ± 57	-14 ± 49		
P, chg within group[d]	0.09	0.12	0.98	0.04	0.35	0.002		
P, difference between groups[a]	0.63		0.11		0.07		0.20	0.45
6 minute walk distance (those who walked 6 min) (m)[f]								
No. in analysis	141	245	96	194	39	127		
BL, mean ± SD[c]	323 ± 67	339 ± 80	333 ± 63	340 ± 77	332 ± 69	350 ± 73		
Chg (FU-BL), mean ± SD	6 ± 45	6 ± 45	0 ± 50	-4 ± 45	5 ± 52	-14 ± 49		
P, chg within group[d]	0.13	0.06	0.99	0.23	0.58	0.002		
P, difference between groups[a]	0.89		0.13		0.09		0.20	0.45
Grip strength (kg), females[g]								
No. in analysis	81	122	55	99	23	63		
BL, mean ± SD[c]	19.3 ± 5.7	18.6 ± 6.5	18.7 ± 6.0	19.3 ± 6.1	20.2 ± 5.0	20.0 ± 6.0		
Chg (FU-BL), mean ± SD	-0.2 ± 4.2	-1.0 ± 5.3	-1.1 ± 4.7	-1.3 ± 5.0	-1.9 ± 5.8	-2.2 ± 5.3		
P, chg within group[d]	0.67	0.03	0.09	0.008	0.14	0.002		
P, difference between groups[a]	0.26		0.89		0.63		0.61	0.76
Grip strength (kg), males[g]								
No. in analysis	99	177	70	143	31	96		
BL, mean ± SD[c]	28.6 ± 9.2	30.9 ± 9.1	29.5 ± 9.7	31.3 ± 9.0	33.0 ± 8.0	31.9 ± 8.8		
Chg (FU-BL), mean ± SD	-0.6 ± 6.4	-0.2 ± 5.2	-1.4 ± 7.6	-1.3 ± 7.0	-2.1 ± 5.0	-2.8 ± 4.8		
P, chg within group[d]	0.34	0.65	0.13	0.03	0.03	<0.001		
P, difference between groups[a]	0.51		0.92		0.38		0.61	0.76

Abbreviations: BL = baseline, CI = confidence interval, FU = follow-up, IU/d = international units per day; SD = standard deviation.

[a]A longitudinal mixed effects linear regression model with fixed effects including a single term for treatment, 3 time point terms, and 3 treatment-by-time interaction terms and a random intercept for participant was fit for each outcome; this model included all available measures of the outcome for all participants, including those with only a baseline measure. Each time-specific P value for difference between dose groups is derived from the corresponding treatment-by-time interaction term. The interaction P test for overall difference between groups in differential change from baseline is from a 3-degree of freedom test of the combined 3 treatment-by-time interaction terms from the longitudinal model. The Benjamini-Hochberg procedure was used to control

the false discovery rate to less than 1/9 (1 out of the maximum number of overall comparisons in each family of analyses (table or figure) comparing dose groups; an adjusted P value is statistically significant if <0.11.

[b]The Short Physical Performance Battery (SPPB) is a 3-part assessment of physical functioning: balance testing, timed 4-meter walk, and ability to stand up from a seated position in a chair; each part is scored 0 to 4 and the total SPPB score (range 0 to 12) is the sum of the 3 subscores. Higher scores indicate better physical function. The total balance stand time (range 0-30 s) combines the stand durations from the 3 balance tests. Gait speed was calculated as 4 meters divided by the duration of the walk in seconds. The chair stand test outcome is the time required to complete 5 chair stands and the test is terminated if not completed in 60 seconds or less.

[c]Baseline values are shown for those with a follow-up measure at the given time point.

[d]P values for time-specific change within group were derived from t-tests.

[e]The Timed Up and Go (TUG) test is a timed test of standing up from a chair, walking at normal pace for 3 meters, turning, returning to the chair, and sitting down; the test result is the time in seconds to complete all 5 parts. The test is terminated at 60 seconds if not complete by that time.

[f]The 6-minute walk is a test of endurance; the participant is instructed to walk at maximum pace for 6 minutes and the score is distance covered. Each site used a straight line course 10 meters in length; each end was marked with a cone which the participant had to walk around. Total distance walked was recorded for each participant who started the walk.

[g]Grip strength is the maximum of 3 tries with the dominant hand of a hand-held dynamometer; if the dominant hand could not be tested, results for the non dominant hand were used.

eTable 5. Exploratory analysis: Change in functional outcome measures since randomization in the 4-group analysis population (those randomized before any adaptation of the randomization probabilities)[a]

	3 months				12 months				24 months				P, interaction[b]	
	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	Unadj	Adj (signif. if <0.11)
SPPB score[c]														
No. in analysis	64	63	62	193	57	49	45	182	50	11	14	152		
BL, mean ± SD[d]	8.4 ± 2.5	8.1 ± 2.4	8.7 ± 2.3	8.8 ± 2.3	8.4 ± 2.5	8.2 ± 2.3	8.6 ± 2.2	8.8 ± 2.2	8.4 ± 2.6	8.8 ± 1.9	9.1 ± 1.5	9.0 ± 2.3		
Chg (FU-BL), mean ± SD	0.1 ± 1.7	0.1 ± 2.0	-0.1 ± 1.9	0.1 ± 1.9	0.4 ± 1.7	0.0 ± 1.9	0.0 ± 2.3	-0.1 ± 1.9	-0.4 ± 2.6	-0.3 ± 2.1	-0.7 ± 1.5	-0.7 ± 2.3		
P, chg within group[e]	0.72	0.58	0.68	0.49	0.11	0.94	0.95	0.59	0.30	0.68	0.11	<0.001		
P, v. 200 IU/d[b]	0.33	0.92	0.94	--	0.13	0.14	0.99	--	0.47	0.50	0.32	--	0.84	0.93
Total SPPB balance stand time (s)[c]														
No. in analysis	64	63	62	192	57	49	45	181	50	11	14	151		
BL, mean ± SD[d]	26.9 ± 6.5	26.1 ± 6.1	27.1 ± 5.1	26.4 ± 6.8	27.1 ± 6.7	26.5 ± 5.2	26.7 ± 5.4	26.9 ± 6.4	27.1 ± 7.0	26.9 ± 3.8	25.7 ± 6.4	26.6 ± 6.9		
Chg (FU-BL), mean ± SD	-0.2 ± 5.6	1.2 ± 6.3	-0.7 ± 4.2	0.5 ± 6.7	-0.1 ± 5.1	1.2 ± 6.1	-0.6 ± 7.7	0.3 ± 6.7	-2.3 ± 8.1	-1.9 ± 8.4	-1.3 ± 6.7	-0.8 ± 8.5		
P, chg within group[e]	0.81	0.14	0.22	0.27	0.90	0.17	0.61	0.60	0.05	0.46	0.49	0.22		
P, v. 200 IU/d[b]	0.56	0.47	0.50	--	0.71	0.68	0.36	--	0.49	0.16	0.51	--	0.67	0.93
SPPB gait speed (m/s)[c]														
No. in analysis	63	62	61	191	56	47	43	180	47	11	14	146		
BL, mean ± SD[d]	0.81 ± 0.25	0.80 ± 0.23	0.87 ± 0.22	0.88 ± 0.21	0.81 ± 0.25	0.81 ± 0.23	0.86 ± 0.22	0.88 ± 0.22	0.82 ± 0.26	0.87 ± 0.17	0.91 ± 0.14	0.92 ± 0.21		
Chg (FU-BL), mean ± SD	0.01 ± 0.16	0.00 ± 0.16	0.03 ± 0.19	0.00 ± 0.17	0.03 ± 0.18	-0.03 ± 0.13	-0.03 ± 0.16	-0.02 ± 0.20	0.00 ± 0.17	-0.01 ± 0.13	-0.02 ± 0.11	-0.08 ± 0.20		
P, chg within group[e]	0.51	0.95	0.26	0.90	0.28	0.10	0.18	0.14	0.92	0.84	0.44	<0.001		
P, v. 200 IU/d[b]	0.03	0.63	0.81	--	0.01	0.09	0.85	--	0.27	0.01	0.10	--	0.05	0.36
SPPB chair stands time (s)[c]														
No. in analysis	54	52	53	173	49	40	39	155	37	10	13	115		
BL, mean ± SD[d]	15.8 ± 4.4	16.5 ± 4.5	16.8 ± 10.6	15.5 ± 5.1	15.6 ± 4.2	16.9 ± 4.6	18.1 ± 12.3	15.5 ± 4.9	15.4 ± 4.3	16.0 ± 3.8	14.3 ± 3.0	14.8 ± 4.3		
Chg (FU-BL), mean ± SD	-0.9 ± 3.8	-0.7 ± 5.1	-2.2 ± 11.3	-0.3 ± 4.7	-2.0 ± 5.3	-1.3 ± 4.3	-4.4 ± 13.7	-0.5 ± 4.9	-1.8 ± 4.5	-1.8 ± 5.3	0.9 ± 3.5	-0.6 ± 3.7		
P, chg within group[e]	0.07	0.34	0.16	0.38	0.01	0.06	0.05	0.19	0.02	0.32	0.37	0.10		
P, v. 200 IU/d[b]	0.94	0.53	0.95	--	0.02	0.11	0.40	--	0.07	0.35	0.17	--	0.08	0.36
TUG time (s)[f]														
No. in analysis	63	61	60	189	55	47	40	180	44	11	13	144		
BL, mean ± SD[d]	12.6 ± 7.1	12.6 ± 5.4	11.2 ± 3.0	11.0 ± 3.8	12.2 ± 6.8	12.1 ± 4.2	11.2 ± 3.1	11.0 ± 3.6	11.6 ± 5.0	11.6 ± 1.9	10.8 ± 1.4	10.5 ± 3.0		
Chg (FU-BL), mean ± SD	-0.6 ± 2.1	-0.2 ± 2.8	-0.4 ± 2.0	0.1 ± 2.7	-0.5 ± 3.1	0.3 ± 2.9	-0.3 ± 1.2	0.2 ± 2.4	0.2 ± 2.6	0.2 ± 2.1	0.8 ± 1.7	1.1 ± 2.5		
P, chg within group[e]	0.02	0.57	0.17	0.54	0.23	0.48	0.19	0.26	0.55	0.75	0.10	<0.001		
P, v. 200 IU/d[b]	0.02	0.07	0.33	--	0.06	0.06	0.92	--	0.33	0.02	0.44	--	0.39	0.88

	3 months				12 months				24 months				P, interaction[b]	
	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	1000 IU/d	2000 IU/d	4000 IU/d	200 IU/d	Unadj	Adj (signif. if <0.11)
6 minute walk distance (all starting walk; m)[g]														
No. in analysis	53	52	52	164	44	39	34	148	36	9	11	117		
BL, mean ± SD[d]	309 ± 83	295 ± 89	330 ± 94	322 ± 87	321 ± 76	303 ± 96	333 ± 98	327 ± 85	321 ± 82	334 ± 83	352 ± 65	344 ± 81		
Chg (FU-BL), mean ± SD	12 ± 50	6 ± 43	0 ± 47	6 ± 42	9 ± 61	-11 ± 47	-11 ± 56	-10 ± 52	7 ± 58	-23 ± 58	-54 ± 84	-11 ± 49		
P, chg within group[e]	0.08	0.30	0.98	0.08	0.31	0.16	0.28	0.03	0.50	0.26	0.06	0.01		
P, v. 200 IU/d[b]	0.33	0.26	0.73	--	0.07	0.04	0.93	--	0.92	0.08	0.71	--	0.36	0.88
6 minute walk distance (all walking 6 min; (m)[g]														
No. in analysis	49	49	50	154	42	36	33	137	35	8	10	115		
BL, mean ± SD[d]	316 ± 73	298 ± 90	338 ± 87	331 ± 78	325 ± 64	310 ± 96	341 ± 88	338 ± 73	328 ± 70	347 ± 78	355 ± 68	348 ± 73		
Chg (FU-BL), mean ± SD	9 ± 45	6 ± 43	1 ± 47	6 ± 38	2 ± 48	-9 ± 42	-11 ± 57	-7 ± 44	2 ± 53	-10 ± 45	-39 ± 71	-11 ± 49		
P, chg within group[e]	0.15	0.32	0.91	0.07	0.78	0.22	0.29	0.06	0.80	0.55	0.11	0.02		
P, v. 200 IU/d[b]	0.30	0.55	0.85	--	0.03	0.19	0.89	--	0.54	0.21	0.83	--	0.93	0.93
Grip strength (kg), females[h]														
No. in analysis	26	25	24	74	22	13	16	72	20	5	6	56		
BL, mean ± SD[d]	19.4 ± 4.7	19.4 ± 5.6	19.2 ± 5.8	19.8 ± 5.8	19.6 ± 4.5	20.6 ± 4.9	19.0 ± 5.6	19.7 ± 5.8	19.4 ± 4.7	20.4 ± 6.7	20.3 ± 5.6	19.7 ± 5.7		
Chg (FU-BL), mean ± SD	0.3 ± 3.4	-1.4 ± 4.3	-0.9 ± 3.6	-1.2 ± 5.3	-2.9 ± 4.6	-1.6 ± 4.9	-1.2 ± 2.7	-1.5 ± 4.9	-1.4 ± 6.0	-0.8 ± 6.6	-2.5 ± 6.7	-2.1 ± 5.4		
P, chg within group[e]	0.65	0.11	0.24	0.05	0.008	0.26	0.09	0.01	0.33	0.80	0.40	0.006		
P, v. 200 IU/d[b]	0.95	0.21	0.66	--	0.72	0.30	0.89	--	0.85	0.61	0.68	--	0.60	0.93
Grip strength (kg), males[h]														
No. in analysis	34	36	39	110	32	32	28	98	27	6	9	87		
BL, mean ± SD[d]	30.8 ± 8.5	31.8 ± 10.3	30.5 ± 9.4	31.0 ± 9.0	31.2 ± 8.4	32.1 ± 10.8	29.5 ± 8.6	31.5 ± 8.7	32.5 ± 8.4	38.7 ± 13.7	28.0 ± 8.4	31.7 ± 9.0		
Chg (FU-BL), mean ± SD	-0.1 ± 3.7	-0.9 ± 5.0	0.4 ± 6.9	-0.5 ± 4.4	-1.6 ± 6.7	-3.1 ± 5.3	-2.6 ± 7.8	-2.3 ± 6.3	-2.0 ± 5.0	-3.0 ± 5.9	-3.3 ± 3.9	-3.1 ± 4.9		
P, chg within group[e]	0.89	0.28	0.73	0.27	0.20	0.002	0.09	0.001	0.05	0.27	0.03	<0.001		
P, v. 200 IU/d[b]	0.94	0.79	0.65	--	0.69	0.46	0.56	--	0.76	0.30	0.82	--	0.79	0.93

Abbreviations: BL = baseline, CI = confidence interval, FU = follow-up, IU/d = international units per day; SD = standard deviation.

[a]For those randomized to 2000 or 4000 IU/d and switched to 1000 IU/d, observation time is limited to time prior to switching.

[b]A longitudinal mixed effects linear regression model with fixed effects including 3 treatment terms, 3 time point terms, and 9 treatment-by-time interaction terms and a random intercept for participant was fit for each outcome; this model included all available measures of the outcome for all participants, including those with only a baseline measure. Each time-specific P value for difference between each higher dose group and control is derived from the corresponding treatment-by-time interaction term. The interaction P test for overall difference between groups in differential change from baseline is from a 9-degree of freedom test of the combined 9 treatment-by-time interaction terms from the longitudinal model. The Benjamini-Hochberg procedure was used to control the false discovery rate to less than 1/9 (1 out

of the maximum number of overall comparisons in each family of analyses (table or figure) comparing dose groups; an adjusted P value is statistically significant if <0.11.

[c]The Short Physical Performance Battery (SPPB) is a 3-part assessment of physical functioning: balance testing, timed 4-meter walk, and ability to stand up from a seated position in a chair; each part is scored 0 to 4 and the total SPPB score (range 0 to 12) is the sum of the 3 subscores. Higher scores indicate better physical function. The total balance stand time (range 0-30 s) combines the stand durations from the 3 balance tests. Gait speed was calculated as 4 meters divided by the duration of the walk in seconds. The chair stand test outcome is the time required to complete 5 chair stands and the test is terminated if not completed in 60 seconds or less.

[d]Baseline values are shown for those with a follow-up measure at the given time point.

[e]P values for time-specific change within group were derived from t-tests.

[f]The Timed Up and Go (TUG) test is a timed test of standing up from a chair, walking at normal pace for 3 meters, turning, returning to the chair, and sitting down; the test result is the time in seconds to complete all 5 parts. The test is terminated at 60 seconds if not complete by that time.

[g]The 6-minute walk is a test of endurance; the participant is instructed to walk at maximum pace for 6 minutes and the score is distance covered. Each site used a straight line course 10 meters in length; each end was marked with a cone which the participant had to walk around. Total distance walked was recorded for each participant who started the walk.

[h]Grip strength is the maximum of 3 tries with the dominant hand of a hand-held dynamometer; if the dominant hand could not be tested, results for the non dominant hand were used.