Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Pre-defined Primary, Secondary, Exploratory, and Biomarkers Outcomes in DO-HEALTH

Endpoints	Outcomes	Time frame
Cardio-vascular	Primary: Systolic and diastolic blood pressure change, measured with a standardized blood pressure assessment in sitting position [1]	Baseline, 12, 24 and 36 months
	Secondary: Incident Hypertension	Over 36 months
	Exploratory: 1. Major cardio-vascular events as a composite endpoint (any event: myocardial infarction, stroke, revascularization procedures of CABG and PCI, incident congestive heart disease, cardiovascular mortality) confirmed by medical records	Over 36 months
	2. Individual major cardio-vascular endpoints (myocardial infarction, stroke, incident congestive heart disease, and cardiovascular mortality) confirmed by medical records	Every 3 months over 36 months
Bone	Primary*: Incident non-vertebral fractures, assessed every 3 months (4 visits, 9 phone calls) and confirmed by medical and/or x-ray reports	Over 36 months
	Secondary: 1. Incident hip fractures, assessed every 3 months (4 visits, 9 phone calls) and based on medical records and/or x-ray reports	Over 36 months
	2. Incident total fractures, combined non-vertebral and vertebral fractures among subgroup of 1503 participants with DXA vertebral morphometry assessment	Over 36 months
	3. Incident vertebral fractures based on DXA vertebral morphometry assessment among 1503 participants with DXA vertebral morphometry assessment	Over 36 months
	4. Bone mineral density decrease at the lumbar spine and hip based on DXA vertebral morphometry among subset of 1503 participants	Over 36 months
	Exploratory: 1. Incident repeat fractures: any repeat non-vertebral fractures in all participants, vertebral fractures and total fractures among subset of 1503 participants with yearly DXA measurements	Over 36 months
	2. Functional recovery after long bone fracture	Over 36 months

Muscle	Primary*: Functional decline (lower extremity function), measured with the Short Physical Performance Battery (SPPB) [2]	Baseline, 12, 24, and 36 months
	Secondary: 1. Rate of falls (any low trauma fall, injurious fall)	Assessed every 3 months over 36 months
	2. Reaction time assessed with the repeated sit-to-stand test (5 repeats as part of the SPPB [2])	Baseline, 12, 24, and 36 months
	3. Grip strength assessed with the Martin Vigorimeter [3]	Baseline, 12, 24, and 36 months
	4. Muscle mass decrease at upper and lower extremities among 1503 participants with DXA measurements	Baseline, 12, 24, and 36 months
	5. Dual tasking 10-meter gait speed	Baseline, 12, 24, and 36 months
	6. Musculoskeletal pain assessed with the McGill questionnaire [4]	Baseline, 12, 24, and 36 months
	Exploratory: 1. Incident sarcopenia among subset of 1503 participants with yearly DXA measurements	Over 36 months
	2. Decline in physical activity assessed by an excerpt from the Nurses' Health Study (NHS) questionnaire [5]	Over 36 months
Brain	Primary: Cognitive decline assessed by the Montreal Cognitive Assessment (MoCA)[6]	Baseline, 12, 24 and 36 months
	Secondary: 1. Mental health decline assessed with an *excerpt* from the Geriatric Depression Scale (GDS) [7,8]	Baseline, 12, 24 and 36 months
	2. Incident Depression assessed with an *excerpt* from the Geriatric Depression Scale (GDS) [7,8]	Over 36 months
	3. Dual tasking gait variability assessed gait analyses and dual task assessments (GAITRite® Platinum, CIR Systems, PA, USA) in a subset of 250 participants. Participants performed 4 walking tasks with and without cognitive challenge[9]	Baseline, 12, 24 and 36 months
	Exploratory: incident dementia, any new diagnosis of dementia (self-reported or proxy-reported) confirmed by medical records	Over 36 months
Immunity	Primary: Rate of any infections, incidence of infections assessed every 3 months by an standardized infection protocol and questionnaire [10,11]	Baseline, and every 3 months up to 36 months
	Secondary:	

	1. Rate of upper respiratory infections and rate of flu-like illness assessed every 3 months by an standardized infection protocol and questionnaire [10,11]	Over 36 months
	2. Incident severe infections that lead to hospital admission assessed every 3 months by an standardized infection protocol and questionnaire [10,11]	Over 36 months
	Exploratory: 1. Incident cancer (any cancer, gastro-intestinal, breast cancer in women, prostate cancer in men) assessed every 3 months and confirmed by medical records	Over 36 months
	2. Rate of implant infections after total hip or knee replacement (due to fracture or osteoarthritis) assessed every 3 months and confirmed by medical records	Over 36 months
	3. Rate of gastro-intestinal infections assessed every 3 months and confirmed by medical records	Over 36 months
Cartilage	Secondary: 1. Severity of knee pain in participants with symptomatic knee osteoarthritis, assessed with the Knee injury and Osteoarthritis Outcome Score (KOOS) [12] questionnaire. Knee OA assessment with modified ACR criteria.	Baseline, 12, 24 and 36 months
	2. Rate of knee buckling, questionnaire-based [13]	Baseline, 12, 24 and 36 months
	3. NSAID use and number of joints with pain assessed by questionnaire and homunculus figure	Baseline, 12, 24 and 36 months
	Exploratory: 1. Incident osteoarthritis: Incident symptomatic knee osteoarthritis ; incident symptomatic hip osteoarthritis; incident symptomatic hand osteoarthritis. Incident hip and knee OA was assessed based on clinical examination (modified ACR criteria for hip [14] and knee OA [15]) and specific questionnaires (KOOS [12], HOOS [16]).	Baseline, 12, 24 and 36 months
	2. Composite endpoint: incident symptomatic knee, hip or hand osteoarthritis	Baseline, 12, 24 and 36 months
	3. severity of hip pain in those with prevalent symptomatic hip osteoarthritis **assessed by the Hip** injury and Osteoarthritis Outcome Score (**HOOS** [16]**)**	Baseline, 12, 24 and 36 months

	4. severity of hand pain in those with prevalent symptomatic hand osteoarthritis assessed by the QuickDASH [17]	Baseline, 12, 24 and 36 months
Dental	Secondary: 1. Decline in oral health assessed with the Geriatric Oral Health Assessment Index (GOHAI) [18] questionnaire	Baseline, 12, 24, and 36 months
	2. Tooth loss assessed by tooth count at every clinical visit	Over 36 months
Gastro-Intestinal	Secondary: rate of GI symptoms assessed with ROME III questionnaire [19,20]	Baseline, 12, 24, and 36 months
Glucose-Metabolic	Secondary: 1. Change in fasting glucose and insulin using calculated using quantitative insulin-sensitivity check index (QUICKI), and the HOMA index [21]	Baseline, 12, 24, and 36 months
	2. Body composition among a subset of 1503 participants with DXA measurements	Baseline, 12, 24, and 36 months
Kidney	Secondary : Decline in kidney function measured by blood creatinine levels and estimated glomerular filtration rate with the Cockcroft-Gault formula [22]	Baseline, 12, 24, and 36 months
Global Health	Secondary: 1. Quality of life assessed with EQ5D-3L (EuroQuol) questionnaire [23]	Every 6 months
	2. Incident frailty assessed with the Survey of Health, Aging and Retirement in Europe - Frailty Instrument (SHARE-FI) [24]	Over 36 months
	3. Incident disability regarding activities of daily living assessed with Health Assessment Questionnaire (PROMIS-HAQ) questionnaire [25]	Baseline, 12, 24 and 36 months
	4. Incident nursing home admission	Over 36 months
	5. Rate of acute hospital admission	Over 36 months
	6. Mortality	Over 36 months
Biomarker endpoints	▪ To support primary and secondary endpoints of the study: (1) Bone: calcium, phosphate, 25(OH)D, intact PTH, calcium/creatinine ratio in second spot urine (*calculated*), Beta-Crosslaps serum, P1NP, albumin (2) Cardiovascular: Troponin T, NT-proBNP, homocysteine, creatin kinase, cholesterol, HDL-cholesterol, nonHDL-cholesterol, LDL-cholesterol, triglycerides (3) Inflammation: high sensitivity CRP, Interleukin 6 (4) Gastrointestinal: AST, ALT, gGT, alkaline phosphatase, bilirubin (5) Glucose-metabolic: fasting glucose, insulin	Baseline, 12, 24, and 36 months

	(6) Kidney: serum creatinine; calcium/creatinine ratio in second spot urine (*calculated*), serum urea, uric acid, albumin urine, total protein, eGFR (*calculated*) (7) Global Health: – Ions: sodium, potassium, chloride, magnesium; – Proteins: total protein, albumin, ferritin, soluble transferrin receptor; – Hormones: TSH, fT4, fT3, cortisol; – Vitamins: folic acid, vitamin B12, 25(OH)D ▪ For novel inflammation and immunity markers (802 participants recruited in Zurich and Basel): (1) *Inflammation:* TNF-α, IL-10, IL-17, IL-22 (2) *Cellular immunity:* CD3, CD4, CD25, CD127 ▪ For novel bone and muscle markers (802 participants recruited in Zurich and Basel): (1) Sclerostin (2) Myostatin	
Adherence laboratory	Serum 25(OH)D concentrations (measured both by an automated assay and HPLCMS/MS) and plasma PUFA concentrations (EPA, AA, DHA; measured by a sensitive and selective assay based on gas chromatography coupled to mass spectrometry detection (GC-MS)) in all participants	Baseline, 12, 24, and 36 months

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eTable 2. Post Hoc Analysis Using Multiply Imputed Data and Site Random Effects

Table 2A. Primary continuous endpoints

	Vitamin D	Vitamin D No Vitamin D	Difference	Omega-3	Omega-3 No Omega-3	Difference	Strength Exercise	Exercise Control Exercise [a]	Difference
	(n=1076)	(n=1081)	(99% CI) P value	(n=1073)	(n=1084)	(99% CI) P value	(n=1081)	(n=1076)	(99% CI) P value
Systolic BP (99% CI)									
Unadjusted baseline	144.2 (142.7, 145.6)	142.9 (141.4, 144.3)	1.3 (-0.8, 3.3) P=0.10	143.2 (141.8, 144.7)	143.9 (142.4, 145.3)	-0.7 (-2.7, 1.4) P=0.41	143.7 (142.2, 145.1)	143.4 (141.9, 144.8)	0.3 (-1.7, 2.4) P=0.69
Adjusted change from baseline [b]									
Year I	-7.9 (-10.3, -5.5)	-7.5 (-9.9, -5.1)	-0.4 (-2.1, 1.2) P=0.52	-7.8 (-10.2, -5.4)	-7.6 (-10.0, -5.2)	-0.2 (-1.8, 1.4) P=0.77	-7.3 (-9.7, -4.8)	-8.1 (-10.5, -5.7)	0.9 (-1.0, 2.7) P=0.23
Year II	-8.5 (-10.9, -6.2)	-7.5 (-9.9, -5.1)	-1.0 (-2.7, 0.6) P=0.11	-8.6 (-11.0, -6.2)	-7.5 (-9.9, -5.0)	-1.1 (-2.8, 0.6) P=0.09	-7.8 (-10.3, -5.4)	-8.2 (-10.6, -5.8)	0.4 (-1.4, 2.2) P=0.59
Year III	-8.8 (-11.3, -6.3)	-7.4 (-9.9, -4.9)	-1.4 (-3.3, 0.5) P=0.05	-8.7 (-11.2, -6.3)	-7.5 (-10.0, -5.0)	-1.3 (-3.1, 0.6) P=0.08	-8.0 (-10.5, -5.5)	-8.2 (-10.7, -5.8)	0.3 (-1.6, 2.1) P=0.71
Across all 3 years	-8.4 (-10.7, -6.1)	-7.5 (-9.8, -5.2)	-0.9 (-2.2, 0.4) P=0.08	-8.3 (-10.6, -6.0)	-7.5 (-9.9, -5.2)	-0.8 (-2.1, 0.5) P=0.12	-7.7 (-10.0, -5.3)	-8.2 (-10.5, -5.9)	0.5 (-0.9, 2.0) P=0.34
Diastolic BP (99% CI)									
Unadjusted baseline	75.7 (74.9, 76.5)	76.0 (75.2, 76.8)	0.3 (-0.8, 1.4) P=0.47	75.8 (75.0, 76.6)	75.9 (75.2, 76.7)	-0.1 (-1.2, 1.0) P=0.77	75.9 (75.1, 76.7)	75.9 (75.1, 76.6)	0.1 (-1.6, 1.2) P=0.89
Adjusted change from baseline [b]									
Year I	-3.0 (-4.7, -1.3)	-3.1 (-4.9, -1.4)	0.1 (-0.8, 1.0) P=0.71	-3.3 (-5.0, -1.5)	-2.9 (-4.6, -1.1)	-0.4 (-1.3, 0.5) P=0.25	-2.7 (-4.5, -1.0)	-3.4 (-5.2, -1.7)	0.7 (-0.3, 1.7) P=0.07
Year II	-3.3 (-5.1, -1.6)	-3.2 (-4.9, -1.4)	-0.2 (-1.1, 0.8) P=0.68	-3.5 (-5.3, -1.8)	-3.0 (-4.7, -1.2)	-0.6 (-1.6, 0.4) P=0.10	-3.3 (-5.0, -1.5)	-3.2 (-5.0, -1.5)	-0.1 (-1.0, 0.9) P=0.85
Year III	-3.6 (-5.3, -1.8)	-3.4 (-5.2, -1.6)	-0.2 (-1.1, 0.8) P=0.63	-3.8 (-5.6, -2.1)	-3.1 (-4.9, -1.4)	-0.7 (-1.7, 0.3) P=0.06	-3.5 (-5.2, -1.7)	-3.5 (-5.3, -1.8)	0.1 (-0.9, 1.0) P=0.85
Across all 3 years	-3.3 (-5.0, -1.6)	-3.2 (-4.9, -1.6)	-0.1 (-0.8, 0.7) P=0.87	-3.5 (-5.2, -1.8)	-3.0 (-4.7, -1.3)	-0.6 (-1.3, 0.2) P=0.05	-3.1 (-4.8, -1.4)	-3.4 (-5.1, -1.7)	0.3 (-0.5, 1.1) P=0.34
Montreal Cognitive Assessment (99% CI) [c]									
Unadjusted baseline	25.8 (25.5, 26.0)	25.6 (25.3, 25.8)	0.2 (-0.1, 0.6) P=0.11	25.7 (25.4, 25.9)	25.7 (25.4, 25.9)	-0.0 (-0.4, 0.4) P=0.87	25.7 (25.4, 25.9)	25.65 (25.4, 25.9)	0.0 (-0.4, 0.4) P=0.88
Adjusted change from baseline [b]									
Year I	0.2 (-0.6, 1.0)	0.4 (-0.4, 1.2)	-0.2 (-0.5, 0.1) P=0.05	0.3 (-0.5, 1.1)	0.4 (-0.4, 1.2)	-0.1 (-0.3, 0.2) P=0.49	0.3 (-0.5, 1.1)	0.4 (-0.5, 1.2)	-0.0 (-0.3, 0.2) P=0.69
Year II	0.4 (-0.4, 1.2)	0.5 (-0.3, 1.3)	-0.1 (-0.4, 0.2) P=0.33	0.4 (-0.4, 1.2)	0.5 (-0.3, 1.3)	-0.1 (0.4, 0.2) P=0.47	0.5 (-0.3, 1.3)	0.4 (-0.4, 1.2)	0.1 (-0.1, 0.4) P=0.2
Year III	0.3 (-0.5, 1.6)	0.4 (-0.4, 1.3)	-0.0 (-0.3, 0.3) P=0.72	0.4 (-0.4, 1.2)	0.4 (-0.5, 1.2)	0.0 (-0.3, 0.3) P=0.83	0.3 (-0.5, 1.1)	0.4 (-0.4, 1.2)	-0.1 (-0.4, 0.2) P=0.31
Across all 3 years	0.3 (-0.5, 1.1)	0.5 (-0.4, 1.3)	-0.1 (-0.4, 0.1) P=0.16	0.4 (-0.4, 1.2)	0.4 (-0.4, 1.2)	-0.1 (-0.3, 0.2) P=0.59	0.4 (-0.4, 1.2)	0.4 (-0.4, 1.2)	-0.0 (-0.2, 0.2) P=0.92

	Vitamin D (n=272)	Placebo (n=270)	Difference (99% CI) P value	Omega-3 (n=269)	Placebo (n=270)	Difference (99% CI) P value	Strength Exercise (n=267)	Placebo (n=270)	Difference (99% CI) P value
Short Physical Performance Battery (99% CI) [d]									
Unadjusted baseline	10.9 (10.7, 11.2)	10.9 (10.7, 11.1)	0.0 (-0.3, 0.3) P=0.88	10.9 (10.7, 11.2)	10.9 (10.7, 11.1)	0.0 (-0.3, 0.3) P=0.89	10.8 (10.5, 11.0)	10.9 (10.7, 11.1)	-0.1 (-0.5, 0.2) P=0.30
Adjusted change from baseline [b]									
Year I	-0.2 (-0.5, 0.1)	0.0 (-0.3, 0.3)	-0.2 (-0.4, 0.1) P=0.06	-0.1 (-0.4, 0.3)	0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.2) P=0.46	-0.1 (-0.4, 0.3)	0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.2) P=0.55
Year II	-0.0 (-0.4, 0.3)	-0.0 (-0.4, 0.3)	-0.0 (-0.3, 0.3) P=0.92	-0.1 (-0.4, 0.2)	-0.0 (-0.4, 0.3)	-0.1 (-0.4, 0.2) P=0.44	-0.0 (-0.4, 0.3)	-0.0 (-0.4, 0.3)	0.0 (-0.3, 0.3) P=0.97
Year III	-0.1 (-0.57, 0.2)	-0.1 (-0.4, 0.2)	-0.0 (-0.3, 0.3) P=0.79	-0.0 (-0.4, 0.3)	-0.1 (-0.4, 0.2)	0.1 (-0.2, 0.4) P=0.44	-0.2 (-0.6, 0.1)	-0.1 (-0.4, 0.2)	-0.1 (-0.4, 0.2) P=0.26
Across all 3 years	-0.1 (-0.4, 0.2)	-0.0 (-0.3, 0.3)	-0.1 (-0.1, 0.3) P=0.31	-0.1 (-0.4, 0.2)	-0.0 (-0.3, 0.3)	-0.0 (-0.2, 0.2) P=0.77	-0.1 (-0.4, 0.2)	-0.0 (-0.3, 0.3)	-0.1 (-0.3, 0.2) P=0.47

Abbreviations: BP, blood pressure; CI, confidence interval.

[a] Flexibility is the control exercise program.

[b] Regression models were adjusted for age, sex, prior falls, body mass index, number of visit, and corresponding baseline measure, and the random effect of study site. Models were based on complete, imputed data, and adjusted for correlated residuals across time within participants. Changes by year are changes from baseline to the end of that year. Changes across all 3 years are the mean, main effect, of three annual changes from baseline.

[c] A significant time-by-treatment interaction (P=0.04) was found only for the effect of strength exercise on the Montreal Cognitive Assessment, so that strength exercise effects on the Montreal Cognitive Assessment should be viewed on a year-by-year basis rather than across all 3 years. The Montreal Cognitive Assessment was used to assess cognitive decline. The Montreal Cognitive Assessment is a one-page 30-point test that covers several cognitive domains (visuospatial/executive skills, attention, naming, memory, delayed recall, attention, language, abstraction, orientation to time, and place). Positive changes indicate improvement in cognitive function over time.

[d] Significant treatment interactions were found for the Short Physical Performance Battery. Therefore, treatment indicators were included for each of the 8 combinations of treatments in the regression models and each intervention group (with neither of the other two interventions present) was compared to the 270 participants who received none of the 3 intervention. The Short Physical Performance Battery was used to assess muscle function. The Short Physical Performance Battery is a brief performance-based test that includes walking speed, repeated chair stands, and a balance test. Its three components are scored between 0 to 4, with 4 indicating the highest level of performance, and are summed up to yield an overall score (maximum of 12 points). Negative changes indicate decrease in muscle function over time.

Table 2B. Primary count endpoints

	Vitamin D		Omega-3		Exercise	
	Vitamin D	**No Vitamin D**	**Omega-3**	**No Omega-3**	**Strength Exercise**	**Control Exercise [a]**
Nonvertebral fractures [b]						
N of participants	1076	1081	1073	1084	1081	1076
N of fractures	129	127	136	120	133	123
Incidence rate	0.04	0.04	0.04	0.04	0.04	0.04
(99% CI) per person year	(0.03, 0.05)	(0.03, 0.05)	(0.03, 0.06)	(0.03, 0.05)	(0.03, 0.05)	(0.03, 0.05)
Incidence Rate Ratio	1.03		1.17		1.07	
(99% CI)	(0.75, 1.43)		(0.85, 1.62)		(0.77, 1.47)	
P value [d]	0.79		0.20		0.62	

	Vitamin D	Placebo [c]	Omega-3	Placebo [c]	Strength Exercise	Placebo [c]
All infections [e]						
N of participants	272	270	269	270	267	270
N of infections	786	825	716	825	841	825
Incidence rate	1.00	1.05	0.93	1.05	1.09	1.05
(99% CI) per person year	(0.79, 1.26)	(0.83, 1.32)	(0.73, 1.18)	(0.83, 1.32)	(0.87, 1.38)	(0.83, 1.32)
Incidence Rate Ratio	0.95		0.89		1.04	
(99% CI)	(0.84, 1.08)		(0.78, 1.01)		(0.92, 1.19)	
P value [d]	0.33		0.02		0.38	

Abbreviation: CI, confidence interval.

[a] Flexibility is the control exercise program.

[b] Fractures were assessed every 3 months and confirmed by X-ray reports or medical records that describe an X-ray report of the fracture or mention the repair of the fracture.

[c] Estimates are from unadjusted Poisson regression models of nonvertebral fracture and infection counts across 3 years.

[d] Rates and P-values from Poisson regression models of nonvertebral fracture and infection counts across 3 years. Models were adjusted for the fixed effects of age, sex, prior falls, and body mass index, and the random effect of trial site. A significant treatment interaction between vitamin D and omega-3 was found for infections (P=0.01). Therefore, treatment indicators were included for each of the 8 combinations of treatments in the regression models for infections.

[e] Infections were assessed every 3 months. Participants were asked whether any infection with or without fever had occurred. Every case of infection was confirmed by medical records.

eTable 3. Mortality and Nursing Home Admission in the 3-Year Follow-up of DO-HEALTH by Treatment Group

			Vitamin D			Omega-3			Exercise		
		Total	VitD	No VitD		n-3s	No n-3s		Strength Exercise	Control Exercise	
	n		(n=1076)	(n=1081)	*p*-value	(n=1073)	(n=1084)	*p*-value	(n=1081)	(n=1076)	*p*-value
Death, n (%)[a]	2157	25 (1.2)	12 (1.1)	13 (1.2)	0.85	8 (0.7)	17 (1.6)	0.07	11 (1.0)	14 (1.3)	0.54
Nursing home, n (%)[a]	2157	22 (1.0)	13 (1.2)	9 (0.8)	0.39	11 (1.0)	11 (1.0)	0.98	13 (1.2)	9 (0.8)	0.39
.											

eTable 4. Adherence to the Study Medication and Exercise Programs [n, (%)] in DO-HEALTH by Treatment Group

A. Among participants answering the compliance questionnaire at least once during the time period

	Took at least 80% of pills				Performed exercise at least two times per week		Performed exercise at least three times per week	
Time	**Vitamin D**	**No Vitamin D**	**n-3s**	**No n-3s**	**Strength Exercise**	**Control Exercise**	**Strength Exercise**	**Control Exercise**
Year 1	953/1043 (91.4)	934/1050 (89.0)	927/1033 (89.7)	960/1060 (90.6)	804/1053 (76.4)	829/1040 (79.7)	697/1053 (66.2)	746/1040 (71.7)
Year 2	844/966 (87.4)	828/968 (85.5)	822/950 (86.5)	850/984 (86.4)	670/967 (69.3)	681/967 (70.4)	571/967 (59.1)	606/967 (62.7)
Year 3	800/964 (83.0)	760/968 (78.5)	772/945 (81.7)	788/987 (79.8)	593/971 (61.1)	625/961 (65.0)	510/971 (52.5)	563/961 (58.6)

n-3s= omega-3 fatty acids.

B. Among all participants assuming noncompliance for both nonrespondants and those without follow-up

	Took at least 80% of pills				Performed exercise at least two times per week		Performed exercise at least three times per week	
Time	**Vitamin D (n=1076)**	**No Vitamin D (n=1081)**	**n-3s (n=1073)**	**No n-3s (n=1084)**	**Strength Exercise (n=1081)**	**Control Exercise (n=1076)**	**Strength Exercise (n=1081)**	**Control Exercise (n=1076)**
Year 1	953 (88.6)	934 (86.4)	927 (86.4)	960 (88.6)	804 (74.4)	829 (77.0)	697 (64.5)	746 (69.3)
Year 2	844 (78.4)	828 (76.6)	822 (76.6)	850 (78.4)	670 (62.0)	681 (63.3)	571 (52.8)	606 (56.3)
Year 3	800 (74.4)	760 (70.3)	772 (72.0)	788 (72.7)	593 (54.9)	625 (58.1)	510 (47.2)	563 (52.3)

n-3s= omega-3 fatty acids.

eTable 5. Average Absolute Changes in Serum 25(OH)D, DHA, and EPA Levels in the Main Effects Groups

	Vitamin D (n=1076)	No Vitamin D (n=1081)	n-3s (n=1073)	No n-3s (n=1084)	Strength Exercise (n=1081)	Control Exercise (n=1076)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
25(OH)D, ng/mL						
BL	22.4 (8.4)	22.4 (8.5)	22.4 (8.4)	22.4 (8.4)	22.8 (8.6)	22 (8.3)
T1	33.7 (8.9)	21.6 (8.7)	27 (10.2)	28.2 (11)	27.9 (10.4)	27.3 (10.8)
T2	35.9 (10.1)	22.5 (9.1)	28.6 (11.5)	29.8 (11.9)	29.7 (11.5)	28.7 (11.9)
T3	37.6 (11.3)	24.4 (10.2)	30.6 (12.3)	31.3 (12.9)	31.3 (12.1)	30.7 (13.1)
DHA, µg/mL						
BL	78.1 (37.9)	78.1 (35.9)	78.9 (37.2)	77.3 (36.6)	78.2 (36.5)	78 (37.4)
T1	124.5 (58.6)	126.4 (59.8)	161 (54.8)	91.2 (40.2)	125.5 (58.5)	125.5 (60)
T2	103.7 (47.3)	105.9 (50)	135.1 (44.8)	75.4 (31.2)	104.6 (48.7)	105 (48.7)
T3	105.2 (51.7)	105.9 (48.9)	135.6 (49.6)	76.3 (29.4)	105.9 (52)	105.1 (48.6)
EPA, µg/mL						
BL	30.6 (21.5)	31.1 (19.9)	30.8 (20)	30.9 (21.4)	30.6 (20.8)	31.1 (20.6)
T1	51.6 (32.9)	54.2 (33.7)	71.5 (32.8)	35 (22.3)	52.8 (33.1)	53 (33.6)
T2	46.7 (29.2)	48.8 (30.2)	64.1 (30.2)	31.9 (18.5)	47.4 (29.7)	48.1 (29.7)
T3	48.8 (30.1)	49.3 (29.7)	64.7 (30.5)	33.8 (19.7)	49.3 (30.6)	48.7 (29.1)

25(OH)D= 25-hydroxyvitamin D. DHA= docosahexaenoic acid. EPA= eicosapentaenoic acid. n-3s= omega-3 fatty acids..

eTable 6. Effects of Treatments on Type of Infections in the 3-Year Follow-up of DO-HEALTH by Treatment Group

A. Individual effects

	Vitamin D	Placebo	Omega-3	Placebo	Strength Exercise	Placebo
Infections, any (N=6233)						
Incidence rate (95% CI) per person year	1.01 (0.92, 1.10)	1.06 (0.96,1.15)	0.94 (0.85, 1.03)	1.06 (0.96, 1.15)	1.10 (1.01, 1.20)	1.06 (0.96, 1.15)
Incidence Rate Ratio (95% CI)	0.95 (0.84, 1.08)		0.89 (0.78, 1.01)		1.04 (0.92, 1.18)	
p-value	0.33		0.02		0.38	
Gastrointestinal infections (N=401)						
Incidence rate (95% CI) per person year	0.05 (0.03, 0.08)	0.04 (0.03,0.07)	0.06 (0.04, 0.08)	0.04 (0.03, 0.07)	0.06 (0.04, 0.09)	0.04 (0.03, 0.07)
Incidence Rate Ratio (95% CI)	1.15 (0.66, 1.98)		1.25 (0.73, 2.14)		1.36 (0.80, 2.31)	
p-value	0.52		0.29		0.13	
Urinary infections (N=620)						
Incidence rate (95% CI) per person year	0.07 (0.05, 0.09)	0.11 (0.08,0.14)	0.04 (0.03, 0.06)	0.11 (0.08, 0.14)	0.10 (0.08, 0.13)	0.11 (0.08, 0.14)
Incidence Rate Ratio (95% CI)	0.64 (0.42, 0.96)		0.38 (0.23, 0.62)		0.95 (0.66, 1.38)	
p-value	0.004		<.0001		0.74	

	Vitamin D	No Vitamin D	Omega-3	No Omega-3	Strength Exercise	Control Exercise
Upper respiratory infections (N=2755)						
Incidence rate (95% CI) per person year	0.44 (0.41, 0.47)	0.44 (0.41,0.48)	0.42 (0.39, 0.45)	0.46 (0.43, 0.50)	0.43 (0.40, 0.46)	0.45 (0.42, 0.48)
Incidence Rate Ratio (95% CI)	0.99 (0.90, 1.09)		0.90 (0.81, 0.99)		0.96 (0.87, 1.06)	
p-value	0.79		0.005		0.34	
Lower respiratory infections (N=1077)						
Incidence rate (95% CI) per person year	0.15 (0.14, 0.17)	0.17 (0.15,0.19)	0.16 (0.15, 0.18)	0.16 (0.14, 0.18)	0.17 (0.15, 0.19)	0.15 (0.14, 0.17)
Incidence Rate Ratio (95% CI)	0.91 (0.78, 1.07)		1.05 (0.89, 1.23)		1.08 (0.93, 1.27)	
p-value	0.14		0.45		0.19	

B. Combined effects

		Vitamin D + Omega-3	Vitamin D + Strength Exercise	Omega-3 + Strength Exercise	Omega-3 + Vitamin D + Strength Exercise
Infections, all (N=6233)	Incidence Rate Ratio (95% CI)	0.98 (0.86, 1.11)	0.95 (0.84, 1.08)	0.90 (0.79, 1.03)	0.92 (0.81, 1.05)
	p-value	0.67	0.34	0.04	0.10
Upper respiratory infections (N=2755)	Incidence Rate Ratio (95% CI)	0.89 (0.77,1.02)	0.95 (0.83, 1.10)	0.87 (0.75, 0.99)	0.86 (0.72, 1.02)
	p-value	0.03	0.38	0.007	0.02
Lower respiratory infections (N=1077)	Incidence Rate Ratio (95% CI)	0.96 (0.76, 1.12)	0.99 (0.79, 1.23)	1.13 (0.91, 1.42)	1.04 (0.79, 1.36)
	p-value	0.61	0.90	0.14	0.74
Gastrointestinal infections (N=401)	Incidence Rate Ratio (95% CI)	1.04 (0.72, 1.50)	1.22 (0.85, 1.75)	1.08 (0.75, 1.55)	1.17 (0.75, 1.82)
	p-value	0.80	0.16	0.59	0.37
Urinary infections (N=620)	Incidence Rate Ratio (95% CI)	0.75 (0.56, 1.01)	1.01 (0.76, 1.36)	0.92 (0.69, 1.23)	0.84 (0.58, 1.20)
	p-value	0.01	0.90	0.46	0.20

Incidence rates, incidence rate ratios, and P-values from Poisson regression models of all infections, as well as the most commonly occurring infection types (upper respiratory, lower respiratory, gastrointestinal, urinary), across 3 years. Models were adjusted for the fixed effects of age, sex, prior falls, body mass index, and study site.

eTable 7. P-Values for Interactions

	Interaction terms p-values			
	Vitamin D [a]	**Omega-3 [a]**	**Strength Exercise [a]**	**All groups [b]**
Systolic				
Age (<75 vs ≥75 years)	0.64	0.08	0.995	
Sex	0.01	0.73	0.001	
Vitamin D (<20 vs ≥20 ng/mL)	0.23	0.23	0.13	
DHA+EPA (<100 vs ≥100 µg/mL)	0.79	0.87	0.90	
Infections				
Age (<75 vs ≥75 years)				0.004
Sex				0.17
Vitamin D (<20 vs ≥20 ng/mL)				0.19
DHA+EPA (<100 vs ≥100 µg/mL)				0.002

DHA=docosahexaenoic acid. EPA=eicosapentaenoic acid.
[a] Interaction between the 3 main treatment groups and listed subgroups.
[b] Interaction between the 8 treatment group combinations and listed subgroups.

eTable 8. Mean Calcium, Parathyroid Hormone (PTH), and Estimated Glomerular Filtration Rate (eGFR) Levels in the 3 Year Follow-up of DO-HEALTH by Treatment Group

A. Calcium Levels, mmol/l

		Vitamin D (n=1076)	No Vitamin D (n=1081)	Omega-3 (n=1073)	No Omega-3 (n=1084)	Strength Exercise (n=1081)	Control Exercise (n=1076)
Baseline	Mean (SD)	2.37 (0.09)	2.37 (0.09)	2.37 (0.09)	2.37 (0.09)	2.37 (0.09)	2.38 (0.09)
	≥2.6 mmol/L, n (%)	14/1069 (1.3)	12/1072 (1.1)	15/1064 (1.4)	11/1077 (1.0)	14/1072 (1.3)	12/1069 (1.1)
Year 1	Mean (SD)	2.33 (0.09)	2.32 (0.09)	2.32 (0.09)	2.32 (0.09)	2.32 (0.09)	2.33 (0.09)
	≥2.6 mmol/L, n (%)	2/953 (0.2)	3/965 (0.3)	3/942 (0.3)	2/976 (0.2)	2/956 (0.2)	3/962 (0.3)
Year 2	Mean (SD)	2.33 (0.08)	2.32 (0.08)	2.33 (0.09)	2.32 (0.08)	2.32 (0.08)	2.33 (0.09)
	≥2.6 mmol/L, n (%)	5/915 (0.6)	4/916 (0.4)	5/901 (0.6)	4/930 (0.4)	4/923 (0.4)	5/908 (0.6)
Year 3	Mean (SD)	2.34 (0.09)	2.33 (0.09)	2.33 (0.09)	2.33 (0.09)	2.33 (0.09)	2.33 (0.09)
	≥2.6 mmol/L, n (%)	3/914 (0.3)	9/915 (1.0)	7/900 (0.8)	5/929 (0.5)	5/916 (0.6)	7/913 (0.8)

*none of the participants had a calcium level above 3.0 mmol/L at any point during the study

B. PTH Levels, ng/l

		Vitamin D (n=1076)	No Vitamin D (n=1081)	Omega-3 (n=1073)	No Omega-3 (n=1084)	Strength Exercise (n=1081)	Control Exercise (n=1076)
Baseline	Mean (SD)	46.9 (16.3)	47.0 (17.6)	47.3 (16.5)	46.6 (17.4)	47.4 (17.8)	46.5 (16.1)
Year 1	Mean (SD)	47.3 (16.0)	52.1 (18.5)	50.8 (18.5)	48.6 (16.3)	49.8 (17.3)	49.6 (17.6)
Year 2	Mean (SD)	47.7 (16.3)	52.9 (19.9)	51.1 (18.9)	49.5 (17.8)	50.2 (18.5)	50.3 (18.3)
Year 3	Mean (SD)	46.5 (15.9)	51.9 (22.0)	49.7 (19.5)	48.6 (19.3)	49.0 (19.0)	49.3 (19.8)

C. eGFR, mL/min/1.73m2

		Vitamin D (n=1076)	No Vitamin D (n=1081)	Omega-3 (n=1073)	No Omega-3 (n=1084)	Strength Exercise (n=1081)	Control Exercise (n=1076)
Baseline	Mean (SD)	62.9 (10.3)	62.8 (10.4)	63.0 (10.4)	62.6 (10.2)	62.9 (10.4)	62.7 (10.3)
Year 1	Mean (SD)	62.7 (10.7)	63.4 (10.8)	63.2 (10.9)	62.8 (10.6)	63.3 (10.7)	62.8 (10.8)
Year 2	Mean (SD)	62.4 (10.2)	62.7 (10.6)	62.8 (10.6)	62.3 (10.2)	62.7 (10.6)	62.4 (10.2)
Year 3	Mean (SD)	62.0 (10.6)	62.6 (10.7)	62.6 (11.0)	62.0 (10.4)	62.5 (10.7)	62.1 (10.7)

eTable 9. Adverse Events in the DO-HEALTH by Treatment Group

A. Vitamin D Adverse Events

Adverse Event (ICD-10, version 2010 when trial was ongoing).	Total (n=2157)	Vitamin D (n=1076)	No Vitamin D (n=1081)	HR (95% CI)
Disorders of mineral metabolism (E83.X)	28 (1.3%)	15 (1.4%)	13 (1.2%)	
Kidney stones (N20.X)	15 (0.7%)	7 (0.7%)	8 (0.7%)	
Total	43	17	26	0.71 (0.38-1.31)

HR= hazard ratio.

B. Omega-3 Adverse Events

Adverse Event (ICD-10, version 2010 when trial was ongoing).	Total (n=2157)	Omega-3 (n=1073)	No Omega-3 (n=1084)	HR (95% CI)
Gastrointestinal symptoms, i.e. dyspepsia, gastritis and duodenitis, gastro-esophageal reflux disease, abdominal and pelvic pain, symptoms of peptic ulcer, nausea, constipation, diarrhea (K30, K29.X, K21.X, R10.X, K25.X, K27.X, R11. K59.X, K58.X. K52.X).	458 (21.2%)	207 (19.3%)	251 (23.5%)	
Bleeding, i.e. hemaetemesis, hematuria, superficial injuries involving multiple body regions, haemorrhage from respiratory passages (K92.X, N02.X, R31, T14.X, T00.X, R04.X)	181 (8.4%)	80 (7.5%)	101 (9.3%)	
Atrial fibrillation or other irregular rhythms (I48, I49.X)	145 (6.7%)	78 (7.3)	67 (6.2%)	
Total*	683	322	361	0.90 (0.77-1.05)

**Some participants had more than one type of adverse event.*
HR= hazard ratio. ICD-10= International Statistical Classification of Diseases and Related Health Problems, 10th revision coding.

C. Exercise Adverse Events

Adverse Event (ICD-10, version 2010 when trial was ongoing).	Total (n=2157)	Strength Exercise (n=1081)	Control Exercise (n=1076)	HR (95% CI)
Increased muscle pain (M79.X)	284 (13.2%)	125 (11.6%)	159 (14.8%)	
Increased joint pain (M25.X)	442 (20.5%)	217 (20.1%)	225 (20.9%)	
Dizziness (R42)	156 (7.2%)	79 (7.3%)	77 (7.2%)	
Tendon lesions (M66.X)	9 (0.4%)	2 (0.2%)	7 (0.7%)	
Total*	745	361	384	0.97 (0.84-1.13)

**Some participants had more than one type of adverse event.*
HR= hazard ratio. ICD-10= International Statistical Classification of Diseases and Related Health Problems, 10th revision coding.

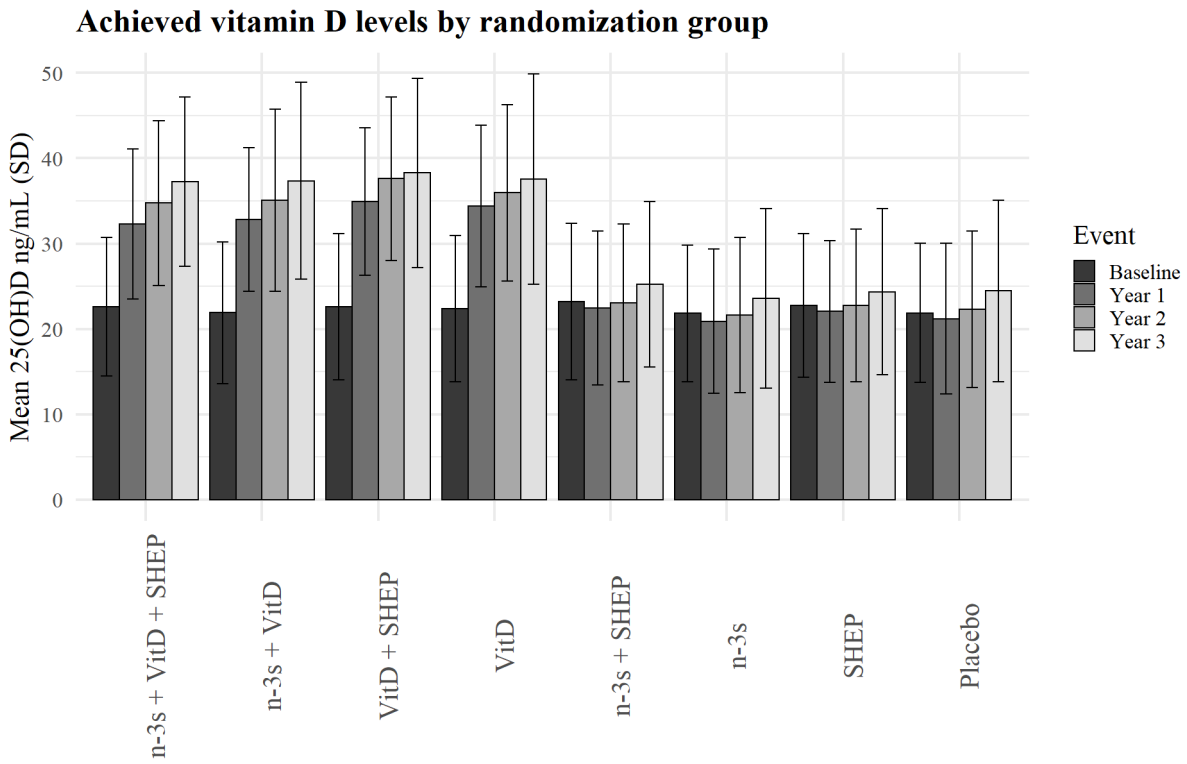
D. Safety measurements during follow-up

	Cases of Adverse Events, n (%)			Cases of Adverse Events, n (%)		
	Vitamin D (n=1076)	**No Vitamin D (n=1081)**	**HR (95% CI)**	**Omega-3 (n=1073)**	**No Omega-3 (n=1084)**	**HR (95% CI)**
Hypercalcemia, CA≥2.6 mmol/L,	8	11	0.77 (0.31-1.92)	11	8	1.47 (0.59-3.67)
PTH≥65 ng/l	204	284	0.71 (0.59-0.84)	257	231	1.23 (1.03-1.48)
PTH≤15 ng/l	2	3	0.72 (0.12-4.37)	3	2	1.98 (0.31-12.59)
eGFR≤30 mL/min per 1.73m^2	4	3	1.37 (0.30-6.32)	2	3	0.40 (0.07-2.18)

eGFR= estimated glomerular filtration rate. HR= hazard ratio. PTH= parathyroid hormone.

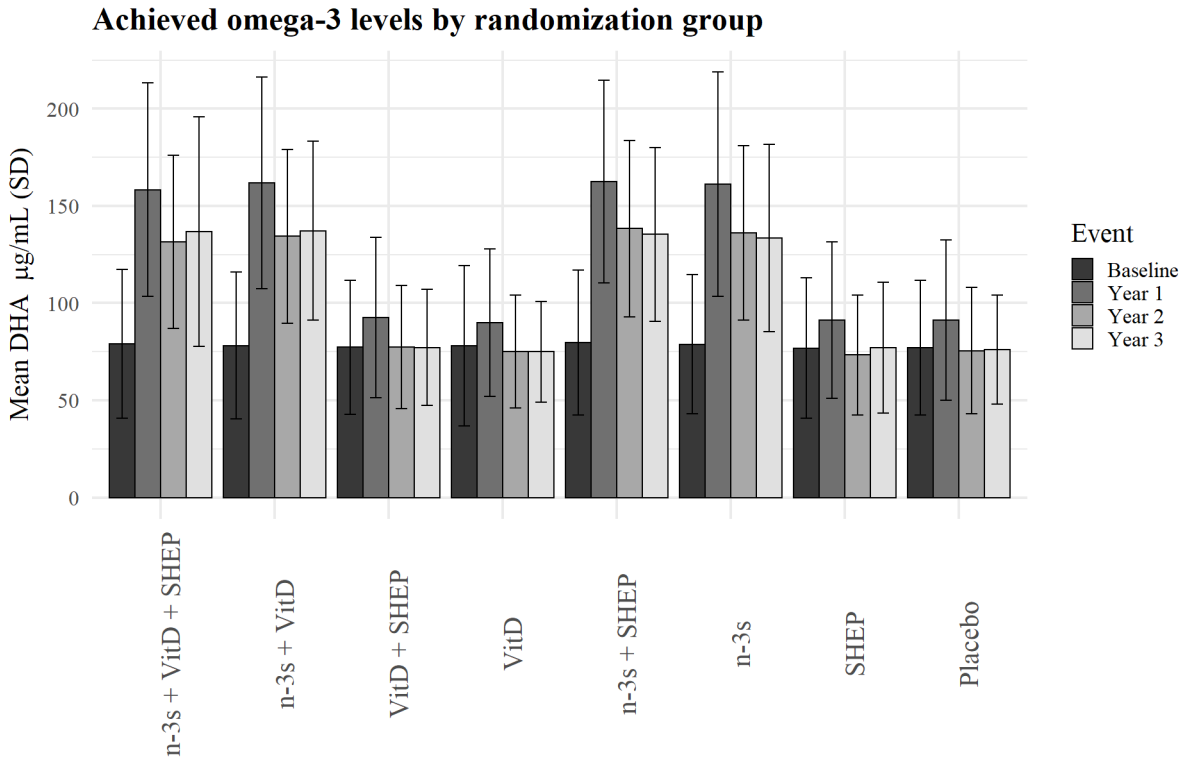
eFigure 1. Serum Changes in 25(OH)D, DHA and EPA by the 8 Treatment Arms

A. 25(OH)D, ng/mL



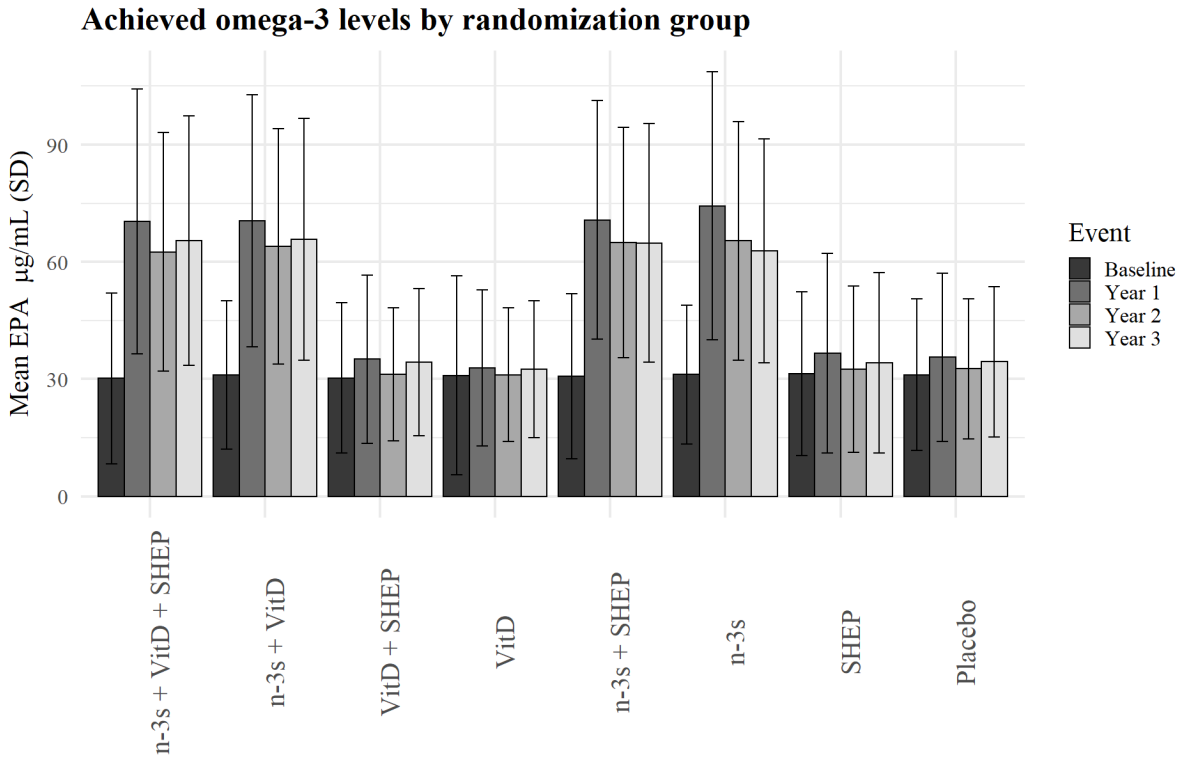
25(OH)D= 25-hydroxyvitamin D. n-3s= omega-3 fatty acids. SHEP= strength-training exercise program. VitD= vitamin D.

B. DHA, µg/mL



DHA= docosahexaenoic acid. n-3s= omega-3 fatty acids. SHEP= strength-training exercise program. VitD= vitamin D.

C. EPA, µg/mL



EPA= eicosapentaenoic acid. n-3s= omega-3 fatty acids. SHEP= strength-training exercise program. VitD= vitamin D.

eFigure 2A. Subgroup Analysis of Effect of Treatment on Systolic Blood Pressure and Infections by Sex and Age (see next page)

The two primary outcomes with the greatest intervention effects, systolic blood pressure and infections, were examined for subgroup effects.

Abbreviations: CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio.

[a]Number of participants randomized to each treatment group.

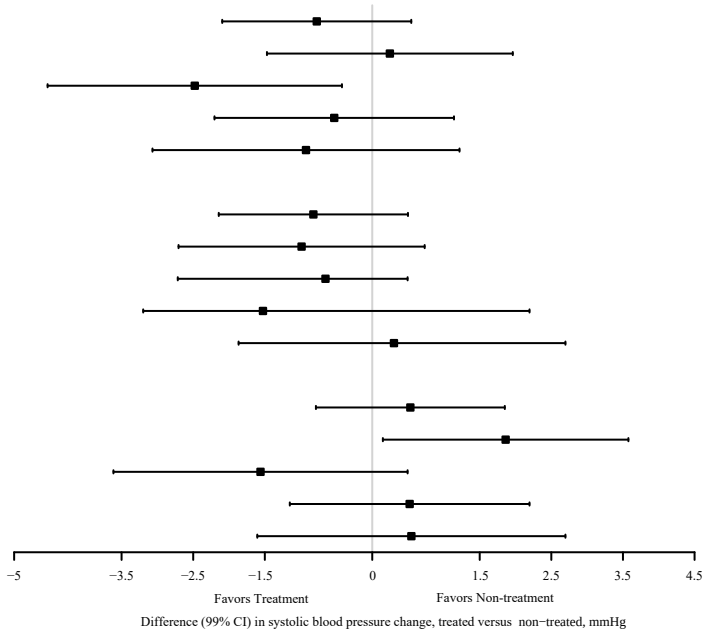
[b]Unadjusted values.

[c]Adjusted values. For change in systolic blood pressure, differences are from repeated measures linear regression models in the primary analysis with correlated residuals across time within participants, and adjusted for the fixed effects of age, sex, prior fall, body mass index, number of visit, study site, and baseline systolic blood pressure. The plot shows differences of least square means from repeated measures linear regression model with changes from baseline at 1, 2, and 3 years as outcomes compared to changes in the non-treated group (e.g. vitamin D versus no vitamin D). For infections, results are from the 8 combinations of treatments groups in the primary analysis. The plot shows the incidence rate ratio per person-year from a Poisson regression model with infection count across 3 years as the outcome adjusted for the fixed effects of age, sex, prior fall, body mass index, study site, and offset of log person-years. Error bars show 99% confidence intervals.

[d]Infections were assessed via questionnaire every 3 months and verified by an independent physician using all available information, including symptoms present, treatment received, and general practitioner diagnosis and hospitalization record, if available.

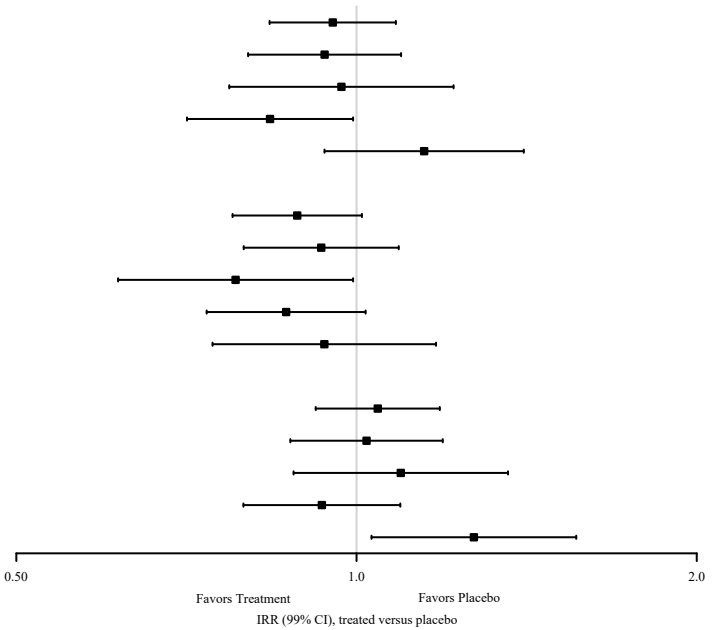
eFIGURE 2A.A: Subgroup analysis of systolic blood pressure by sex and age group

Group	N[a]	Mean at BL (99% CI)[b]		Mean at T3 (99% CI)[b]		Absolute difference, T3−BL (99% CI)[b]		Adjusted difference (99% CI)[c]
Vitamin D	Treated | Non−treated	Treated	Non−treated	Treated	Non−treated	Treated	Non−treated	Treated vs. Non−Treated
All	1076 | 1081	144.2 (142.7, 145.6)	142.9 (141.5, 144.3)	134.9 (133.3, 136.4)	135.5 (134.0, 137.1)	−9.5 (−11.0, −8.0)	−7.6 (−9.2, −6.0)	−0.8 (−2.1, 0.5)
Women	667 | 664	143.0 (141.1, 145.0)	142.1 (140.2, 144.0)	133.7 (131.7, 135.7)	134.1 (132.1, 136.0)	−9.7 (−11.7, −7.7)	−8.5 (−10.5, −6.4)	0.2 (−1.5, 2.0)
Men	409 | 417	146.0 (143.9, 148.1)	144.2 (142.1, 146.3)	136.7 (134.3, 139.1)	137.9 (135.4, 140.3)	−9.2 (−11.6, −6.9)	−6.2 (−8.6, −3.8)	−2.5 (−4.5, −0.4)
Age 70−74	606 | 631	144.4 (142.4, 146.4)	142.2 (140.4, 144.1)	134.2 (132.2, 136.2)	134.6 (132.7, 136.5)	−10.3 (−12.3, −8.3)	−7.5 (−9.4, −5.5)	−0.5 (−2.2, 1.1)
Age 75+	470 | 450	143.9 (141.7, 146.0)	143.9 (141.7, 146.1)	135.8 (133.4, 138.2)	136.9 (134.4, 139.5)	−8.5 (−10.8, −6.2)	−7.8 (−10.4, −5.3)	−0.9 (−3.1, 1.2)
Omega−3								
All	1073 | 1084	143.2 (141.8, 144.6)	143.9 (142.4, 145.3)	134.3 (132.8, 135.8)	136.1 (134.6, 137.6)	−9.0 (−10.6, −7.4)	−8.1 (−9.6, −6.6)	−0.8 (−2.1, 0.5)
Women	668 | 663	142.3 (140.4, 144.3)	142.8 (140.9, 144.7)	132.6 (130.6, 134.5)	135.2 (133.2, 137.1)	−9.8 (−11.9, −7.7)	−8.4 (−10.3, −6.5)	−1.0 (−2.7, 0.7)
Men	405 | 421	144.6 (142.6, 146.7)	145.5 (143.3, 147.7)	137.0 (134.6, 139.3)	137.6 (135.1, 140.1)	−7.8 (−10.4, −5.3)	−7.6 (−9.9, −5.4)	−0.7 (−2.7, 1.4)
Age 70−74	635 | 602	142.7 (140.9, 144.6)	143.8 (141.8, 145.8)	133.4 (131.5, 135.3)	135.5 (133.5, 137.5)	−9.1 (−11.2, −7.0)	−8.5 (−10.5, −6.6)	−1.5 (−3.2, 0.1)
Age 75+	438 | 482	143.9 (141.6, 146.1)	143.9 (141.8, 145.8)	135.6 (133.1, 138.2)	136.9 (134.5, 139.4)	−8.8 (−11.4, −6.3)	−7.6 (−9.9, −5.2)	0.3 (−1.9, 2.5)
Strength Exercise								
All	1081 | 1076	143.7 (142.2, 145.2)	143.4 (141.9, 144.8)	135.5 (134.0, 137.1)	134.9 (133.4, 136.4)	−8.6 (−10.2, −7.1)	−8.5 (−10.0, −7.0)	0.5 (−0.8, 1.9)
Women	665 | 666	142.5 (140.6, 144.5)	142.6 (140.7, 144.6)	134.9 (132.9, 136.9)	132.9 (131.0, 134.8)	−8.1 (−10.1, −6.1)	−10.0 (−12.1, −8.0)	1.9 (0.1, 3.6)
Men	416 | 410	145.6 (143.4, 147.8)	144.6 (142.5, 146.7)	136.5 (134.1, 138.9)	138.0 (135.6, 140.5)	−9.4 (−11.8, −6.9)	−6.1 (−8.4, −3.8)	−1.6 (−3.6, 0.5)
Age 70−74	622 | 615	143.6 (141.6, 145.5)	143.0 (141.0, 144.9)	134.7 (132.8, 136.6)	134.1 (132.1, 136.1)	−8.9 (−10.8, −6.9)	−8.8 (−10.9, −6.7)	0.5 (−1.2, 2.2)
Age 75+	459 | 461	143.8 (141.6, 146.1)	143.9 (141.8, 146.0)	136.7 (134.1, 139.3)	136.0 (133.6, 138.3)	−8.3 (−10.8, −5.7)	−8.0 (−10.3, −5.8)	0.5 (−1.6, 2.7)



eFIGURE 2A.B: Subgroup analysis of infections by sex and age group

Group	N[a]	Number of infections[d]		Crude IR (99% CI)[b]		Adjusted IRR (99% CI)[c]
Vitamin D only	Treated | Placebo	Treated	Placebo	Treated	Placebo	Treated vs Placebo
All	272 | 270	786	825	1.04 (0.95, 1.14)	1.10 (1.00, 1.20)	0.95 (0.84, 1.08)
Women	170 | 165	536	560	1.12 (1.00, 1.25)	1.21 (1.08, 1.34)	0.94 (0.80, 1.10)
Men	102 | 105	250	265	0.90 (0.76, 1.06)	0.92 (0.78, 1.08)	0.97 (0.77, 1.22)
Age 70−74	139 | 155	407	542	1.06 (0.93, 1.21)	1.23 (1.10, 1.38)	0.84 (0.71, 0.99)
Age 75+	133 | 115	379	283	1.02 (0.89, 1.16)	0.91 (0.78, 1.06)	1.15 (0.94, 1.41)
Omega−3 only						
All	269 | 270	716	825	0.97 (0.88, 1.06)	1.10 (1.00, 1.20)	0.89 (0.78, 1.01)
Women	166 | 165	508	560	1.11 (0.99, 1.25)	1.21 (1.08, 1.34)	0.93 (0.79, 1.09)
Men	103 | 105	208	265	0.73 (0.61, 0.87)	0.92 (0.78, 1.08)	0.78 (0.61, 0.99)
Age 70−74	165 | 155	478	542	1.05 (0.94, 1.19)	1.23 (1.10, 1.38)	0.87 (0.74, 1.02)
Age 75+	104 | 115	238	283	0.83 (0.70, 0.98)	0.91 (0.78, 1.06)	0.94 (0.75, 1.18)
Strength Exercise only						
All	267 | 270	841	825	1.14 (1.04, 1.24)	1.10 (1.00, 1.20)	1.04 (0.92, 1.18)
Women	161 | 165	544	560	1.22 (1.09, 1.36)	1.21 (1.08, 1.34)	1.02 (0.87, 1.19)
Men	106 | 105	297	265	1.02 (0.88, 1.18)	0.92 (0.78, 1.08)	1.09 (0.88, 1.36)
Age 70−74	152 | 155	502	542	1.18 (1.05, 1.32)	1.23 (1.10, 1.38)	0.93 (0.79, 1.09)
Age 75+	115 | 115	339	283	1.08 (0.94, 1.24)	0.91 (0.78, 1.06)	1.27 (1.03, 1.56)



eFigure 2B. Subgroup Analysis of Effect of Treatment on Systolic Blood Pressure and Infections by Baseline Levels of 25(OH)D and Median Levels of DHA and EPA (see next page)

The two primary outcomes with the greatest intervention effects, systolic blood pressure and infections, were examined for subgroup effects.

Abbreviations: CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio.

[a]Number of participants randomized to each treatment group.

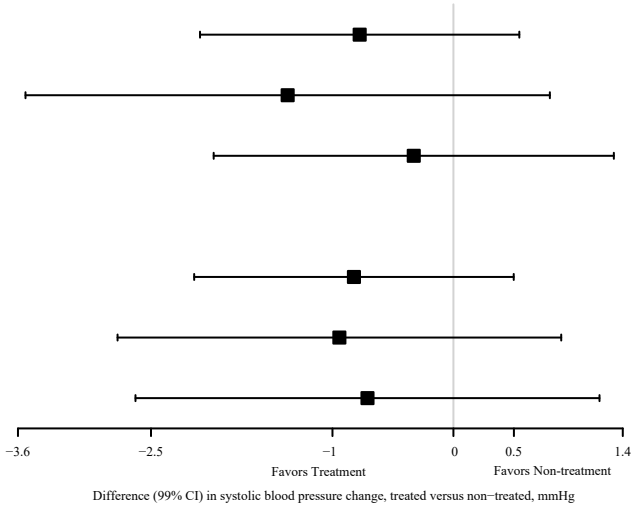
[b]Unadjusted values.

[c]Adjusted values. For change in systolic blood pressure, differences are from repeated measures linear regression models in the primary analysis with correlated residuals across time within participants, and adjusted for the fixed effects of age, sex, prior fall, body mass index, number of visit, study site, and baseline systolic blood pressure. The plot shows differences of least square means from repeated measures linear regression model with changes from baseline at 1, 2, and 3 years as outcomes compared to changes in the non-treated group (e.g. vitamin D versus no vitamin D). For infections, results are from the 8 combinations of treatments groups in the primary analysis. The plot shows the incidence rate ratio per person-year from a Poisson regression model with infection count across 3 years as the outcome adjusted for the fixed effects of age, sex, prior fall, body mass index, study site, and offset of log person-years. Error bars show 99% confidence intervals.

[d]Infections were assessed via questionnaire every 3 months and verified by an independent physician using all available information, including symptoms present, treatment received, and general practitioner diagnosis and hospitalization record, if available.

eFIGURE 2B.A: Subgroup analysis of systolic blood pressure by baseline 25(OH)D and DHA+EPA levels

Group	N[a]	Mean at baseline (99% CI)[b]		Mean at 3 years (99% CI)[b]		Absolute difference T3−BL (99% CI)[b]		Adjusted difference (99% CI)[c]
Vitamin D	Treated | Non−treated	Treated	Non−treated	Treated	Non−treated	Treated	Non−treated	Treated vs. Non−Treated
All	1076 | 1081	144.2 (142.7, 145.6)	142.9 (141.5, 144.3)	134.9 (133.3, 136.4)	135.5 (134.0, 137.1)	−9.5 (−11.0, −8.0)	−7.6 (−9.2, −6.0)	−0.8 (−2.1, 0.5)
25(OH)D <20 ng/ml	427 | 445	145.7 (143.4, 148.0)	144.6 (142.4, 146.9)	137.0 (134.5, 139.5)	136.5 (134.0, 138.9)	−9.3 (−11.9, −6.7)	−8.0 (−10.6, −5.4)	−1.4 (−3.5, 0.8)
25(OH)D >=20 ng/ml	639 | 629	142.8 (140.9, 144.7)	141.7 (139.9, 143.6)	133.6 (131.6, 135.5)	134.8 (132.9, 136.8)	−9.5 (−11.4, −7.7)	−7.3 (−9.3, −5.3)	−0.3 (−2.0, 1.3)
Omega−3								
All	1073 | 1084	143.2 (141.8, 144.6)	143.9 (142.4, 145.3)	134.3 (132.8, 135.8)	136.1 (134.6, 137.6)	−9.0 (−10.6, −7.4)	−8.1 (−9.6, −6.6)	−0.8 (−2.1, 0.5)
DHA EPA <100µg/ml	528 | 540	143.4 (141.3, 145.5)	144.1 (142.0, 146.2)	134.6 (132.5, 136.8)	136.6 (134.4, 138.8)	−8.4 (−10.6, −6.2)	−7.6 (−9.7, −5.5)	−0.9 (−2.8, 0.9)
DHA+EPA >=100 µg/ml	531 | 538	142.9 (140.8, 144.9)	143.5 (141.5, 145.6)	134.0 (131.8, 136.1)	135.6 (133.4, 137.7)	−9.5 (−11.9 −7.1)	−8.5 (−10.7, −6.4)	−0.7 (−2.6, 1.2)



eFIGURE 2B.B: Subgroup analysis of infections by baseline 25(OH)D and DHA+EPA levels

Group	N[a]	Number of infections[d]		Crude IR (99% CI)[b]		Adjusted IRR (99% CI)[c]
Vitamin D only	Treated | Placebo	Treated	Placebo	Treated	Placebo	Treated vs. Placebo
All	272 | 270	786	825	1.04 (0.95, 1.14)	1.10 (1.00, 1.20)	0.95 (0.84, 1.08)
25(OH)D <20 ng/ml	112 | 113	320	329	1.04 (0.90, 1.20)	1.05 (0.91, 1.21)	0.94 (0.77, 1.15)
25(OH)D >=20 ng/ml	159 | 155	464	484	1.04 (0.92, 1.17)	1.12 (0.99, 1.26)	0.96 (0.81, 1.14)
Omega−3 only						
All	269 | 270	716	825	0.97 (0.88, 1.06)	1.10 (1.00, 1.20)	0.89 (0.78, 1.01)
DHA+EPA <100 µg/ml	129 | 133	375	398	1.04 (0.91, 1.18)	1.09 (0.96, 1.24)	0.95 (0.79, 1.15)
DHA+EPA >=100 µg/ml	138 | 135	335	415	0.90 (0.78, 1.03)	1.08 (0.96, 1.23)	0.82 (0.68, 0.99)