Received: 25 June 2024 | Revised: 24 September 2024 | Accepted: 21 October 2024

DOI: 10.1111/jgs.19266

CLINICAL INVESTIGATION

Journal of the American Geriatrics Society

Effect of vitamin D, omega-3 supplementation, or a home exercise program on muscle mass and sarcopenia: DO-HEALTH trial

Anna K. Eggimann MD, PD Dr. med[1,2] | **Caroline de Godoi Rezende Costa Molino PhD**[1] | **Gregor Freystaetter MD**[1,3] | **Bruno Vellas MD**[4,5,6] | **John A. Kanis MD**[7] | **René Rizzoli MD**[8] | **Reto W. Kressig MD**[9] | **Gabriele Armbrecht MD**[10] | **José A. P. Da Silva MD**[11] | **Bess Dawson-Hughes MD**[12] | **Wei Lang PhD**[1] | **Michael Gagesch MD**[1,3,13] | **Andreas Egli MD**[1,3] | **Heike A. Bischoff-Ferrari MD, MPH**[1,3]

[1]Center on Aging and Mobility, University of Zurich, Zurich, Switzerland

[2]Department of Geriatrics, University Hospital Bern and University of Bern, Bern, Switzerland

[3]University Campus Aging Medicine, City Hospital Zurich–Waid, Zurich, Switzerland

[4]Gérontopôle de Toulouse, Institut du Vieillissement, Center Hospitalo-Universitaire de Toulouse, Toulouse, France

[5]UMR INSERM 1027, University of Toulouse III, Toulouse, France

[6]IHU HealthAge, University Hospital Toulouse and University III Paul Sabatier Toulouse, Toulouse, France

[7]Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia and Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK

[8]Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[9]University Department of Geriatric Medicine Felix Platter, University of Basel, Basel, Switzerland

[10]Klinik für Radiologie, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[11]Centro Hospitalar e Universitário de Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[12]Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts, USA

[13]University Clinic for Aging Medicine, Zurich City Hospital, Zurich, Switzerland

Correspondence
Anna K. Eggimann, PD Dr. med.
Department of Geriatrics University Hospital Bern, Freiburgstrasse 40, CH-3010 Bern, Switzerland.
Email: anna.eggimann@insel.ch

Funding information
Seventh framework program of the European Commission, Grant/Award

Abstract

Background: We aimed to investigate the effect of daily supplemental vitamin D, omega-3s, and a thrice-weekly home exercise program, alone or in combination, on change of appendicular lean muscle mass index (ALMI) and incident sarcopenia in older adults.

Methods: This is a secondary endpoint analysis of a 3-year randomized, double-blind, placebo-controlled trial with a $2 \times 2 \times 2$ factorial design among

See related editorial by Kositsawat and Orkaby in this issue.

Number: 278588; NESTEC; Pfizer; Universität Zürich; DNP; Roche; Streuli

2157 community-dwelling, healthy adults aged 70 + years, from 2012 to 2018 (DO-HEALTH). Participants were randomized to 2000 IU/d vitamin D and/or 1 g/d marine omega-3s and/or exercise. Change in ALMI over 3 years was calculated in all participants who underwent dual energy X-ray absorptiometry (DXA) ($n = 1495$) using mixed effect models. Incident sarcopenia was analyzed based on the Sarcopenia Definitions and Outcomes Consortium in all non-sarcopenic participants ($n = 1940$).

Results: Among 1495 participants (mean age 74.9 (sd 4.4); 63.3% were women; 80.5% were at least moderately physically active at baseline) mean gait speed at baseline was 1.2 m/s (sd 0.3), mean ALMI at baseline was 6.65 (SD 0.95) in women, and 8.01 (SD 0.88) kg/m^2 in men. At year 3, average change of ALMI was −0.09 (sd 0.34) kg/m^2 (−1.35%) in women and − 0.17 (sd 0.33) kg/m^2 (−2.0%) in men. None of the treatments individually or in combination had a benefit on ALMI change compared to control over 3 years, with omega-3s showing a small protective effect on ALMI at year 1 only (−0.021 vs. no-omega-3s −0.066 kg/m^2, $p = 0.001$). Of 1940 non-sarcopenic participants at baseline, 88 (4.5%) developed incident sarcopenia over 3 years. None of the treatments individually or in combination reduced the odds of incident sarcopenia compared with placebo.

Conclusion: Among healthy, physically active older adults, ALMI and incidence of sarcopenia were not improved by treatment of daily 2000 IU vitamin D, daily 1 g omega-3s, or a simple home exercise program compared with control over 3 years.

KEYWORDS

gait speed, grip strength, healthy aging, muscle function, older adults, primary prevention

INTRODUCTION

Reduced appendicular muscle mass is a key criterion for diagnosing sarcopenia.[1] Studies have shown that the appendicular lean muscle mass index (ALMI) decreases annually by 0.7% in women and 0.8% in men among healthy older adults.[2] The prevalence of sarcopenia in this population ranges from 9.9% to 40.4%, depending on the diagnostic criteria used.[3] Sarcopenia in older adults is linked to adverse outcomes, including increased falls, functional decline, and higher rates of hospitalizations.[4,5] Therefore, interventions aimed at preventing muscle loss and sarcopenia are of significant public health importance.

Pathophysiological studies indicate that exercise training exerts direct anti-inflammatory and antioxidant effects through specific signaling pathways, which help mitigate muscle loss.[6] This is reinforced by a comprehensive umbrella review, which found strong evidence supporting the positive impact of resistance training on muscle mass.[7] Additionally, various exercise interventions, including gait, balance, strength, vibration, and home-based exercises, have been shown to increase muscle mass in older adults with sarcopenia.[8]

Key points

- DO-HEALTH is one of the largest multinational trials investigating European community-dwelling older adults filling the gap of knowledge on primary prevention of vitamin D, omega-3s, and home exercise program on muscular health among healthy, older adults over 3 years.
- Among these healthy, physically active older adults, both muscle mass and incidence of sarcopenia were not improved by treatment of daily 2000 IU vitamin D, daily 1 g of omega-3s, or a simple home exercise program compared with control over 3 years.

Why does this paper matter?

The results from our large multinational European DO-HEALTH trial do not support the use of high daily doses of vitamin D or omega-3s supplements for the primary prevention of muscular health in older adults with an overall good health status, an active lifestyle, and without vitamin D deficiency.

Mechanistic studies suggest that vitamin D directly affects muscle through its receptor (VDR) found in muscle tissue.[9] A meta-analysis of trials involving vitamin D supplementation of at least 800 IU indicates that muscle mass significantly improves when vitamin D is combined with exercise training.[10] However, vitamin D supplementation alone, without accompanying exercise or protein supplementation, does not appear to have a significant impact on muscle mass.[11]

Regarding omega-3 fatty acids, mechanistic studies support the direct anabolic effect on muscle by activation of mammalian target of rapamycin (mTOR).[12] Some, but not all, clinical studies support the benefits of omega-3s on muscle mass in humans.[13,14]

In summary, evidence from randomized controlled trials (RCTs) investigating the effects of vitamin D, omega-3s, and exercise on appendicular muscle mass and sarcopenia remains limited and inconsistent. Additionally, there is a lack of data on the individual and combined effects of these strategies in healthy, active older adults.

To the best of our knowledge, no RCTs have evaluated the primary preventive effects of vitamin D, omega-3s, and physical exercise in healthy older European adults.

We therefore tested the effect of daily supplemental of 2000 IU vitamin D, daily supplemental 1 g omega-3s, and a simple strength-based home exercise program (SHEP) three times per week, alone or in combination, on changes in ALMI and the incidence of sarcopenia over 3 years.

METHODS

Study design

This is a secondary endpoint analysis of the Vitamin D3—Omega3—Home Exercise—Healthy Aging Longevity Trial (DO-HEALTH) trial. The prespecified secondary endpoint of change in ALMI over the 3 years follow-up was analyzed according to the protocol including all 1495 participants who underwent dual energy X-ray absorptiometry (DXA) measurement at baseline (Supplementary Material). Incident sarcopenia was a predefined exploratory endpoint of DO-HEALTH including 1940 participants with absence of sarcopenia at baseline.[15]

DO-HEALTH is a multicenter, double-blind, $2 \times 2 \times 2$ factorial design, randomized, placebo-controlled clinical trial designed to support healthy longevity in European older adults aged 70 years and older examining the individual and combined effects of omega-3, vitamin D, and simple home exercise over 3 years of follow-up. The study protocol was approved by ethical and regulatory agencies. The primary trial findings were published elsewhere.[16] In brief, treatment with vitamin D3, omega-3s, or a strength-training exercise program did not result in statistically significant differences in improvement in systolic or diastolic blood pressure, nonvertebral fractures, physical performance, infection rates, or cognitive function.

Participants

Participants were physically active community-dwelling adults aged 70 years recruited from five European countries (Austria, France, Germany, Portugal, and Switzerland) including seven study sites (Zurich, Basel, Geneva, Berlin, Innsbruck, Toulouse, and Coimbra). Main inclusion criteria were the absence of major health events in the 5 years prior to enrollment (i.e., cancer or myocardial infarction), sufficient mobility to visit the study centers without assistance, and an MMSE (Mini-Mental State Examination) score of at least 24. Details on recruitment, randomization, and trial procedures are described elsewhere.[15] All participants signed an informed consent form.

Procedures

Participants were randomly assigned to eight treatment groups including three interventions: (1) 2000 IU/d of vitamin D compared with placebo vitamin D; (2) 1 g/d of omega-3s (330 mg of eicosapentaenoic acid [EPA] plus 660 mg of docosahexaenoic acid [DHA] from marine algae) compared with placebo omega-3s; and (3) a strength-training exercise program of 30 min three times per week compared with an attention control exercise program focused on joint flexibility of 30 min three times a week.[15] Clinical visits were at baseline and at 1, 2, and 3 years of follow-up, and in-person phone calls occurred every 3 months.

Outcomes

Appendicular lean mass index (kg/m^2) was measured among participants from four DO-HEALTH study centers, which were equipped with DXA (dual-enengergy X-ray absorptiometry) scanners (Zurich, Berlin, Toulouse, Coimbra). Standardization of measurements was supervised by the Berlin Charité DO-HEALTH center (GA). Lean tissue mass was measured and ALMI was calculated by the integrated DXA software. Change of ALMI was assessed through annual DXA measurements conducted at baseline, year 1, 2, and 3. For subgroup analyses, we defined low ALMI according to the EWGSOP2 gender-

specific cutoff definitions (women <5.5 kg/m^2, men <7 kg/m^2) measured by DXA.[17]

Incident sarcopenia was defined based on the criteria by the Sarcopenia Definition and Outcome Consortium (SDOC).[18] Thereby, sarcopenia (binary outcome) was defined as low muscle strength and low gait speed according to the SDOC definition applying the recommended cutoffs. Low muscle strength was defined as grip strength <35.5 kg in men and <20 kg in women, respectively.[19] The cutoff of <0.8 m/s was applied for low gait speed (highest gait speed of two trials) for women and men. Details of the assessments are reported in the protocol of the main article.[15]

Statistical analysis

Appendicular lean muscle mass index (ALMI)

Intent to treat analyses were performed including all randomized participants who underwent DXA measurement at baseline. Baseline characteristics of the study population were described overall and by treatment group. Normal distributed continuous variables were presented as mean and standard deviation (SD) and non-normal variables as median and interquartile range (IQR). Categorical variables were presented in frequencies and percentages.

Mixed effects model with three time points were fit for the changes in ALMI from baseline to year 1, 2, and 3. The unstructured dependence structure was specified with study site as fixed effect. Covariate adjustment included age, linear spline at age 85, sex, prior falls, BMI, and baseline measure of ALMI (low vs. normal ALMI). Main effects of treatments—vitamin D3, omega-3s, and SHEP were examined in the mixed effects models due to the lack of significant treatment group interactions (both three-way and three two-way interactions). Effects of treatment group, time (a three level categorical variable), and treatment group by time interactions were examined in the mixed effects models. For the effect of omega-3s, a significant treatment*time interaction was found, thus the interaction term was included in the model.

With a sample size of 750 participants per group, the study is powered (80% power, and 5% significance level) to detect a change in muscle mass of 0.05 kg/m^2 (standard deviation 0.34).

Incident sarcopenia

For the outcome of incident sarcopenia, the analytic dataset was a subset of all DO-HEALTH participants ($n = 2157$) who had no sarcopenia at baseline ($N = 1940$). Incident sarcopenia was determined over the three-year follow up and this dichotomous outcome was analyzed using a multivariable logistic regression model.

For the test of treatment effects, we first checked the significance of treatment group interactions. Due to significant omega-3s*SHEP interaction ($p = 0.01$), the eight-level treatment group variable was examined in the multivariable logistic regression model. Therefore, each treatment group was compared with the placebo group for incident sarcopenia. Models were adjusted for age, linear spline at age 85, sex, prior fall, study site, and BMI. Additionally, an offset of the logarithm of each participant's time in the study was included in the models.

Subgroup analyses

Predefined subgroup analyses for both outcomes of muscle mass and sarcopenia included sex (female vs. male), age group (75+ vs. 70–74 years), ALMI according to EWGSOP2 cutoff definitions[17] at baseline (low vs. normal ALMI), vitamin D status at baseline (deficiency <20 nmol/L vs. non-deficiency), median baseline polyunsaturated fatty acid levels (DHA plus EPA <100 or ≥ 100 μg/mL), and baseline protein intake per weight (below vs. above median). There was no significant interaction between treatment group and any of the subgroups, therefore stratified analyses were not conducted.

The type I error rate was fixed at 5%. All statistical analyses were performed using SAS v9.4 (SAS Institute, Inc., Cary, NC, United States).

RESULTS

Overall, 1495 participants underwent DXA and were analyzed for the ALMI outcome by treatment. Median follow-up time of participants was 3 years. Seventeen participants died during follow-up and 24 participants were lost to follow-up. Mean age was 74.9 (sd 4.4); and 63.3% were women. Baseline characteristics are shown in Table 1. Among these 1495 participants, 551 were recruited from Switzerland, 347 from Germany, 300 from Portugal, and 297 from France. A total of 113 participants (7.3%) had low gait speed at baseline. Similarly, 45 participants (3.0%) had a low grip strength (sex-based cutoffs, see above). Mean ALMI at baseline was 6.65 (SD 0.95) kg/m^2 in women and 8.01 (SD 0.88) kg/m^2 in men. This resulted in 155 participants (10.4%) with low ALMI when applying gender-specific cutoffs. The majority of the participants (78%) engaged in moderate to high physical performance at baseline.

TABLE 1 Baseline characteristics of dual energy X-ray absorptiometry participants ($n = 1495$) for main treatment groups.

	Vitamin D		Omega-3 s		Exercise		
	Vitamin D	No Vitamin D	Omega-3 s	No Omega-3 s	SHEP	Control Exercise	Overall
Characteristics	***n* = 746**	***N* = 749**	***n* = 752**	***n* = 743**	***n* = 751**	***n* = 744**	**n = 1495**
Age, years, mean (sd)	75.0 (4.5)	74.9 (4.4)	74.9 (4.3)	75.0 (4.5)	75.0 (4.4)	74.9 (4.4)	74.9 (4.4)
BMI, kg/m^2, mean (sd)	26.8 (4.4)	26.5 (4.2)	26.8 (4.4)	26.7 (4.4)	26.6 (4.3)	26.6 (4.3)	26.6 (4.3)
Women, *n* (%)	476 (63.8)	470 (62.8)	473 (63.6)	473 (63.0)	473 (63.0)	471 (63.6)	946 (63.3)
Country, *n* (%)							
France	142 (19.0)	155 (20.7)	151 (20.1)	146 (19.7)	148 (19.7)	149 (20.0)	297 (19.9)
Germany	172 (23.1)	175 (23.4)	174 (23.1)	173 (23.3)	176 (23.4)	171 (23.0)	347 (23.2)
Portugal	154 (20.6)	146 (19.5)	151 (20.1)	149 (20.1)	149 (19.8)	151 (20.3)	300 (20.1)
Switzerland	278 (37.3)	273 (36.5)	276 (36.7)	276 (37.0)	278 (37.0)	273 (36.7)	551 (36.9)
Living alone, *n* (%)	299 (40.1)	315 (42.1)	300 (39.9)	314 (42.3)	297 (39.6)	317 (42.6)	614 (41.1)
Education, years, mean (sd)[a]	12.5 (4.6)	12.4 (4.4)	12.3 (4.3)	12.5 (4.7)	12.4 (4.4)	12.4 (4.6)	12.4 (4.5)
Comorbidity score,[b] median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Number of medications, mean (sd)	3.5 (2.9)	3.4 (2.9)	3.4 (2.9)	3.5 (2.9)	3.4 (2.9)	3.4 (2.9)	3.4 (2.9)
SPPB score, median (IQR)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	12.0 (10.0–12.0)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	11.0 (10.0–12.0)
Prior fall, *n* (%)	299 (40.1)	305 (40.7)	300 (39.9)	304 (40.9)	302 (40.2)	302 (40.6)	604 (40.4)
Grip strength, kPa, mean (sd)	48.6 (18.0)	58.6 (17.9)	58.2 (17.9)	59.0 (18.0)	58.7 (17.9)	48.6 (18.1)	58.6 (18.0)
Low grip strength, *n* (%)[c]	25 (3.4)	20 (2.7)	29 (3.9)	16 (2.2)	18 (2.4)	27 (3.6)	45 (3.0)
Appendicular lean muscle mass index, kg/m^2, mean (sd)	7.2 (1.1)	7.2 (1.1)	7.2 (1.1)	7.2 (1.2)	7.2 (1.1)	7.2 (1.1)	7.2 (1.1)
Low ALMI, *n* (%)[d]	70 (9.4)	85 (11.4)	71 (9.4)	84 (11.3)	81 (10.8)	74 (10.0)	155 (10.4)
Gait speed, m/sec, mean (sd)[e]	1.1 (0.2)	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)	1.1 (0.2)	1.2 (0.3)	1.2 (0.25)
Low physical performance, *n* (%)[f]	58 (7.8)	55 (7.3)	61 (8.1)	52 (7.9)	55 (7.3)	58 (7.8)	113 (7.8)
Protein intake below median, *n* (%)[g]	414 (55.5)	408 (54.5)	410 (54.5)	412 (55.5)	417 (55.5)	405 (54–4)	822 (55.0)
Vitamin D deficiency <20 ng/mL, *n* (%)[h]	312 (42.2)	335 (45.0)	323 (43.4)	324 (43.9)	313 (42.1)	334 (45.1)	647 (43.6)
Serum 25-hydroxyvitamin D concentration, mean (SD), ng/ml[h]	21.9 (8.4)	21.8 (8.3)	21.8 (8.4)	21.9 (8.4)	22.3 (8.5)	21.4 (8.2)	21.9 (8.4)
Serum DHA concentration, mean (SD), μg/mLm[i]	80.6 (39.2)	80.7 (37.4)	81.3 (38.5)	80.0 (38.1)	80.8 (37.5)	80.5 (39.1)	80.6 (38.3)
Serum EPA concentration, mean (SD), μg/mLm[i]	32.2 (23.5)	32.9 (21.6)	32.3 (21.8)	32.8 (23.3)	32.3 (22.7)	32.7 (22.5)	32.5 (22.6)
Substitution with omega-3, *n* (%)[i]	379 (51.4)	399 (53.7)	385 (52.0)	393 (53.2)	392 (52.9)	386 (52.2)	778 (52.6)
Physical activity level, *n* (%)							

(Continues)

TABLE 1 (Continued)

Characteristics	Vitamin D		Omega-3 s		Exercise		
	Vitamin D	No Vitamin D	Omega-3 s	No Omega-3 s	SHEP	Control Exercise	Overall
	n = 746	*N* = 749	*n* = 752	*n* = 743	*n* = 751	*n* = 744	n = 1495
None	165 (22.1)	127 (17.0)	144 (19.2)	148 (19.9)	145 (19.3)	147 (19.8)	292 (19.5)
1–2 times/week	226 (30.3)	249 (33.3)	249 (32.0)	235 (31.6)	243 (32.4)	232 (31.2)	475 (31.8))
≥3 times/week	355 (47.6)	372 (49.7)	367 (48.9)	360 (48.5)	362 (48.3)	365 (49.1)	727 (48.7)

Abbreviations: ALMI, appendicular lean muscle mass index; BMI, body mass index; EWGSOP1, European Working Group on Sarcopenia in Older People 1; EWGSOP2, European Working Group on Sarcopenia in Older People 2; IQR, interquartile range; SD, standard deviation; SDOC, Sarcopenia Definitions and Outcomes Consortium; SHEP, simple home exercise program; SPPB, short physical performance battery.

[a] $n = 1493$ ($n = 2$ missing).

[b] Comorbidity by self-administered questionnaire.

[c] Low grip strength defined according to EWGSOP2 as grip strength <27 kg for men, and < 16 kg for women.

[d] Low muscle mass defined according to EWGSOP2 as muscle mass <5.5 kg/m^2 for women, and <7.0 kg/m^2 for men.

[e] $n = 1492$ (missing $n = 3$).

[f] Low physical performance defined according to SDOC as gait speed <0.8 m/s.

[g] Protein intake based on median of current sample.

[h] $n = 1483$ (missing $n = 12$).

[i] $n = 1480$ (missing $n = 15$).

At year 3, average decline of ALMI was −0.09 (SD 0.34) kg/m^2 in women and −0.17 (SD 0.33) kg/m^2 in men. Over 3 years follow-up, vitamin D, omega-3s, and SHEP had no effect on change in ALMI individually or in combination (Figure 1, Panels A-C). Only for omega-3s, there was a statistically significant effect after 1 year of follow-up (omega 3 s −0.021 kg/m2 vs. no-omega-3s −0.066, $p = 0.001$). Table 2 displays detailed results of the overall effects in the three main treatment groups on change of ALMI over 3 years. Notably, we did not find differential treatment effects (no significant interaction) for subgroups by sex, age, ALMI at baseline, vitamin D deficiency, or protein intake at baseline (data not shown).

Of 2110 non-sarcopenic participants at baseline, 88 (4.54%) had incident sarcopenia over 3 year follow-up. Baseline characteristics of these participants with complete follow-up data are shown in Table S1. Characteristics of these 1940 participants are similar to the DXA sample of 1495 participants. Over 3 years follow-up vitamin D, omega-3s, and SHEP had no influence on the odds of incident sarcopenia individually or in combination (Figure 2). Detailed results are shown in Table S2.

DISCUSSION

In this multinational European trial involving generally healthy and vitamin D replete and physically active community-dwelling seniors, interventions with vitamin D, omega-3s, and a simple home exercise program—whether individually or in combination—did not lead to a significant change in ALMI as measured by DXA over 3 years. Likewise, the interventions did not reduce the odds of developing sarcopenia. Although omega-3 fatty acid supplementation showed a positive effect on ALMI at the one-year mark, this benefit was not sustained throughout the three-year follow-up period.

To the best of our knowledge, this is the first larger clinical trial to investigate the effects of vitamin D, omega-3s, and a home exercise program, both individually and in combination, on ALMI and incident sarcopenia. In summary, while the trial did not find significant effects from the intervention, this could be due to the overall good health status of the participants, their active lifestyles, and the slower rate of muscle decline compared to what is typically expected in older adults. Notably, 80.5% of DO-HEALTH participants were at least moderately physically active, and 56.4% were vitamin D replete at baseline. This indicates that the participants in DO-HEALTH were generally healthier than the average for their age group, which is also reflected by their relatively good mobility (as evidenced by low proportion of low gait speed).[20] Moreover, longitudinal studies typically show

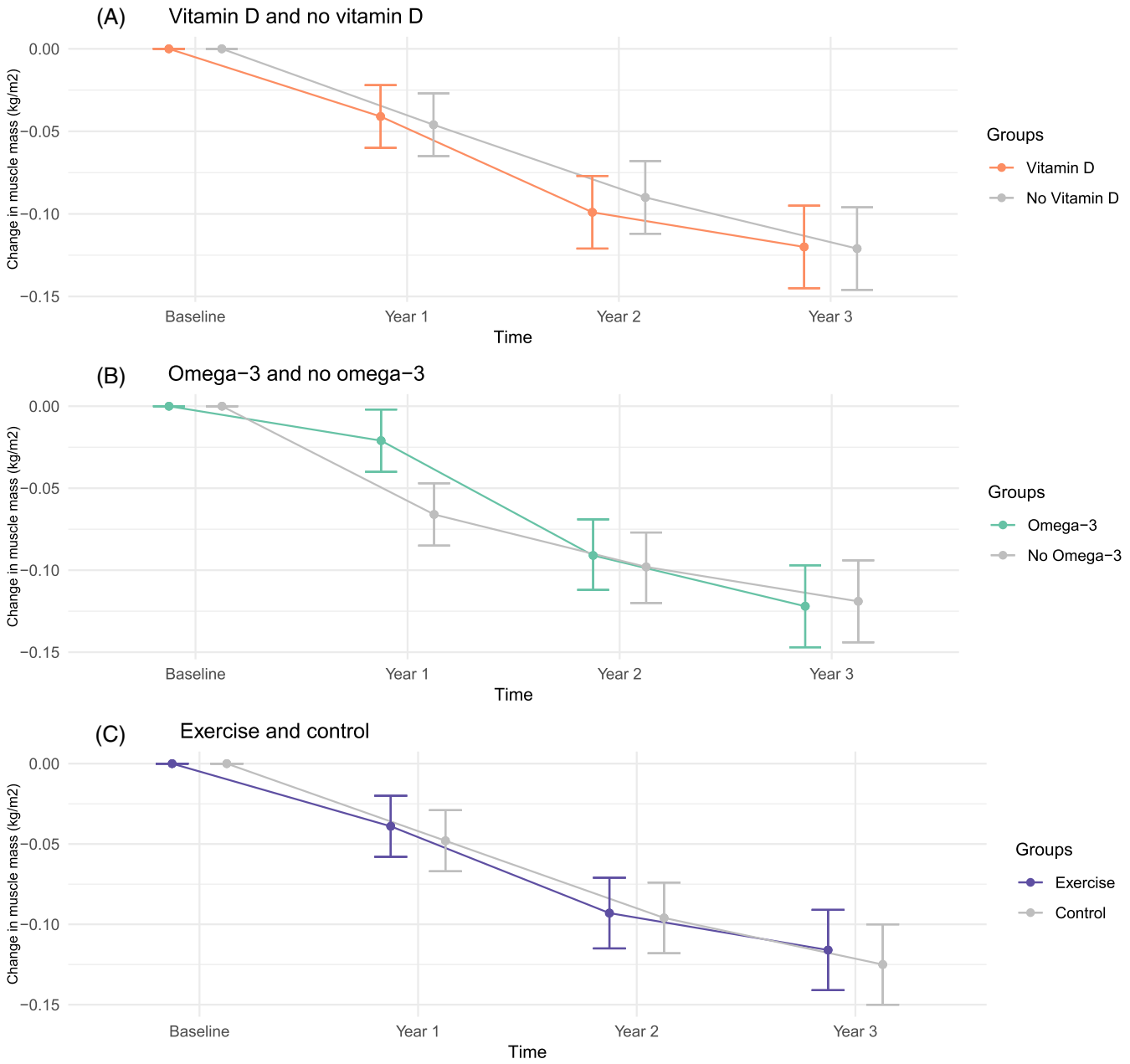

FIGURE 1 Adjusted mean changes of appendicular lean muscle mass index (ALMI) from baseline are presented for the main treatment groups (Vitamin D, Omega-3 s, and Exercise) ($n = 1495$). Covariate adjustment included age, linear spline at age 85, sex, prior falls, BMI, and baseline measure of ALMI (low vs. normal ALMI). Details on the analyses are described in the Methods Section.

that individuals aged 75 and older lose muscle mass at an annual rate of 0.64–0.7% in women and 0.8–0.98% in men.[2] However, in the DO-HEALTH trial, muscle mass decline was slower than expected—only 0.45% per year in women and 0.66% per year in men. This slower-than-expected muscle mass decline suggests that participants were maintaining an active lifestyle and might explain why the home exercise program appeared less impactful. Therefore, our results highlight that an overall active and healthy lifestyle is associated with a lower decline in muscle mass than expected. Therefore, data from DO-HEALTH on muscular health do not contradict the general benefits of exercise for healthy aging.[21] Finally, our results from a large multinational European sample are in line with the US results on vitamin D and omega-3s of the VITAL trial. Of note, data of both the VITAL and DO-HEALTH trials have implications for public health guidelines on the use of vitamin D and omega-3s in generally healthy US and European adults.

For the omega-3 intervention, we observed a small protective effect on muscle mass after 1 year of follow-up, though this effect was not sustained at years 2 and 3. This

TABLE 2 Main treatment effects on appendicular lean muscle mass index (kg/m^2) in the dual energy X-ray absorptiometry sample over 3 years ($n = 1356$).

Adjusted change from baseline to	Vitamin D				Omega-3 s				Exercise			
	Vitamin D (95% CI)	No Vitamin D (95% CI)	Difference (95% CI)	*p*-value	Omega-3 s (95% CI)	No Omega 3 s (95% CI)	Difference (95% CI)	*p*-value	Exercise (95% CI)	Control (95% CI)	Difference (95% CI)	*p*-value
Year 1	−0.041 (−0.060 to −0.022)	−0.046 (−0.065 to −0.027)	0.005 (−0.023 to 0.032)	0.744	−0.021 (−0.040 to −0.002)	−0.066 (−0.085 to −0.047)	0.045 (0.018 to 0.072)	**0.001**	−0.039 (−0.058 to −0.020)	−0.048 (−0.067 to −0.029)	0.009 (−0.018 to 0.036)	0.508
Year 2	−0.099 (−0.121 to −0.077)	−0.090 (−0.112 to −0.068)	−0.008 (−0.040 to 0.022)	0.575	−0.091 (−0.112 to −0.069)	−0.098 (−0.120 to −0.077)	0.007 (−0.023 to 0.039)	0.617	−0.093 (−0.115 to −0.071)	−0.096 (−0.118 to −0.074)	0.003 (−0.028 to 0.034)	0.850
Year 3	−0.120 (−0.145 to −0.095)	−0.121 (−0.146 to −0.096)	0.001 (−0.034 to 0.037)	0.934	−0.122 (−0.147 to −0.097)	−0.119 (−0.144 to −0.094)	−0.002 (−0.038 to 0.033)	0.890	−0.116 (−0.141 to −0.091)	−0.125 (−0.150 to −0.100)	0.010 (−0.026 to 0.045)	0.595
Averaging across 3 years	−0.0876 (−0.104 to −0.069)	−0.086 (−0.103 to −0.068)	−0.001 (−0.026 to 0.024)	0.942	−0.078 (−0.095 to −0.056)	−0.095 (−0.112 to −0.077)	0.017 (−0.008 to 0.042)	0.188	−0.0825 (−0.100 to −0.065)	−0.090 (−0.108 to −0.072)	0.007 (−0.018 to 0.032)	0.573

early benefit aligns with findings from a recent meta-analysis, which reported a muscle mass gain of 0.33 kg (95% CI: 0.05, 0.62) associated with omega-3 supplementation.[14] Notably, the same meta-analysis suggested a potential dose-dependent effect, with more pronounced benefits at higher doses of 2 g/day. In DO-HEALTH, omega-3 supplementation was tested at a dose of 1 g/day, which may help explain the more modest and short-term effects observed in our trial.

Regarding vitamin D, our findings are consistent with a recent meta-analysis that showed no effect of vitamin D on ALMI.[22] Most participants in our study, as well as those in the US VITAL trial[23] were not vitamin D deficient, which may explain the lack of observed benefits. Similarly, both VITAL[23] and DO-HEALTH[24] found no effect of vitamin D on reducing falls. Therefore, data from both trials on primary prevention of muscular health may only apply to selected older adults with an overall good health status and an active lifestyle. In contrast, these results do not contradict the potential benefits of vitamin D on physical function and fall prevention in more vulnerable or vitamin D-deficient older adults.[25]

Regarding incident sarcopenia, 88 participants (4.54%) developed sarcopenia over the three-year period according to the SDOC definition.[26] Previous studies on incident sarcopenia report substantial variation depending on the population studied and the definitions used.[3] For instance, a prospective study among Chinese community-dwelling older adults aged 65 and older reported a 9.0% incidence of sarcopenia over 4 years.[27] In contrast, a study of older adults in Germany found a 4.3% incidence after 3 years,[28] while a study of older Australian men reported a 3.9% incidence after 2 years.[29]

Our study has several strengths. These findings of the DO-HEALTH randomized controlled trial adds important efficacy data to the literature. DO-HEALTH is one of the largest multinational trials investigating European community-dwelling older adults filling the gap of knowledge on primary prevention of vitamin D, omega-3s, and home exercise program among older adults with an overall good health status. ALMI, grip strength, and gait speed have been prospectively measured on a yearly follow-up using validated methods. Thus, we were able to analyze longitudinal data over a three-year period.

There are several limitations to this study. First, while these data are representative for similar community-dwelling older adults with an overall good health status without major comorbidities, findings cannot be generalized to older people with relevant comorbidities or other clinical settings. Moreover, while our sample includes older adults from five European countries, generalizability to other cultural settings is still limited. Second, it is a secondary outcome analysis, thus the analysis may be

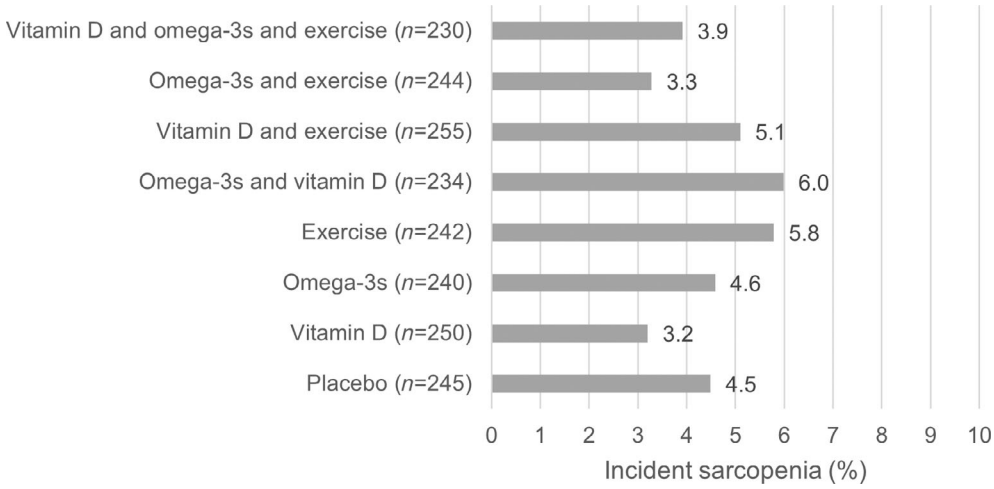

FIGURE 2 Incident sarcopenia in the eight treatment groups over 3 years ($n = 1940$).

underpowered resulting in type 2 error. Third, the majority of study participants already had a moderate to high physical activity level at baseline.[16] Thus, this favorable basic condition of the older adults may limit potential benefit from an additional exercise intervention on muscle health. At the same time, we cannot exclude that a different approach of exercise intervention (e.g., high-intensity, individual, or supervised) may have shown an effect on ALMI and/or incident sarcopenia. Fourth, we defined incident sarcopenia based on the most recent sarcopenia definition by SDOC. However, our results cannot be extrapolated to studies using other definitions of sarcopenia or studies applying other cutoff values of the sarcopenia components. Fifth, while we were able to analyze the overall population of all study sites for the outcome of incident sarcopenia, we were limited for the outcome of ALMI analyzing participants of four study sites that had DXA devices available. However, the risk of selection bias is limited by the randomization process using block randomization stratified by recruitment center, prior fall, sex, and age. We did not adjust for multiple comparison testing for this predefined secondary endpoint of ALMI in the DO-HEALTH trial. Thus, there is a risk of significant findings that occurred by chance. Moreover, a risk of type 2 error remains as this secondary analysis yielded 80% power to detect a change in ALMI of 0.05 kg/m^2. Minimal clinically important difference is not defined for ALMI (kg/m^2) in literature, but described for appendicular skeletal muscle/body mass index ratio as 0.024.[30] Finally, our results cover findings on muscle health of a three-year follow-up. Consequently, these data cannot answer the potential effect of interventions on a long-term perspective (e.g., 10 years).

Our study has several implications to clinical research and practice. Our findings suggest that the interventions do not show a significant change to ALMI measured by DXA. Nevertheless, these results do not exclude that there may be a response of the muscle to the interventions on a microstructural level that cannot be pictured by currently standard methods to measure muscle mass.[31] In addition, for clinical practice it is key to elaborate on the interventions for prevention and treatment of sarcopenia. Currently, programs vary to address sarcopenia and it is for example unclear what specific exercise program (with or without nutritional intervention) is most effective for the management of patients suffering from sarcopenia.[32] Therefore, further interventional studies are needed including vulnerable older adults, who are at particular risk for sarcopenia or suffering from poor muscle health to eventually advance the management of sarcopenia.

In conclusion, the DO-HEALTH trial does not support use of a high daily dose of vitamin D nor omega-3s supplements for the primary prevention of muscular health among healthy, physically active, and vitamin D replete older adults.

AUTHOR CONTRIBUTIONS

Conceptualization: HABF and AKE. Formal analysis: CGRZCM and WL. Funding acquisition: HABF. Methodology and validation: All authors. Writing—original draft: AKE. Writing—review and editing: All authors. All authors meet the ICMJE criteria, and provided final approval to submit the manuscript for publication. The funding/supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We thank all the members of the DO-HEALTH Research Group, and we are grateful to the study participants for their commitment to this study.

FUNDING INFORMATION

The study was funded by the Seventh framework program of the European Commission (Grant Agreement no. 278588, PI Heike A. Bischoff-Ferrari), the University of Zurich (Chair for Geriatric Medicine and Aging Research), DNP, Roche, NESTEC, Pfizer, and Streuli.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Anna K. Eggimann https://orcid.org/0000-0001-8322-5501

REFERENCES

1. Bauer J, Morley JE, Schols A, et al. Sarcopenia: a time for action. An SCWD position paper. *J Cachexia Sarcopenia Muscle*. 2019;10(5):956-961. doi:10.1002/jcsm.12483
2. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Front Physiol*. 2012;3:260. doi:10.3389/fphys.2012.00260
3. Mayhew AJ, Amog K, Phillips S, et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. *Age Ageing*. 2019;48(1):48-56. doi:10.1093/ageing/afy106
4. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. *J Cachexia Sarcopenia Muscle*. 2014;5(4):253-259. doi:10.1007/s13539-014-0161-y
5. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health outcomes of sarcopenia: a systematic review and meta-analysis. *PLoS One*. 2017;12(1):e0169548. doi:10.1371/journal.pone.0169548
6. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle*. 2015;6(3):197-207. doi:10.1002/jcsm.12043
7. Beckwee D, Delaere A, Aelbrecht S, et al. Exercise interventions for the prevention and treatment of sarcopenia. A systematic umbrella review. *J Nutr Health Aging*. 2019;23(6):494-502. doi:10.1007/s12603-019-1196-8
8. Lu L, Mao L, Feng Y, Ainsworth BE, Liu Y, Chen N. Effects of different exercise training modes on muscle strength and physical performance in older people with sarcopenia: a systematic review and meta-analysis. *BMC Geriatr*. 2021;21(1):708. doi:10.1186/s12877-021-02642-8
9. Ceglia L, Niramitmahapanya S, da Silva MM, et al. A randomized study on the effect of vitamin D(3) supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *J Clin Endocrinol Metab*. 2013;98(12):E1927-E1935. doi:10.1210/jc.2013-2820
10. Antoniak AE, Greig CA. The effect of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. *BMJ Open*. 2017;7(7):e014619. doi:10.1136/bmjopen-2016-014619
11. Cheng SH, Chen KH, Chen C, Chu WC, Kang YN. The optimal strategy of vitamin D for sarcopenia: a network meta-analysis of randomized controlled trials. *Nutrients*. 2021;13(10):3589. doi:10.3390/nu13103589
12. Dupont J, Dedeyne L, Dalle S, Koppo K, Gielen E. The role of omega-3 in the prevention and treatment of sarcopenia. *Aging Clin Exp Res*. 2019;31(6):825-836. doi:10.1007/s40520-019-01146-1
13. Ma WJ, Li H, Zhang W, et al. Effect of n-3 polyunsaturated fatty acid supplementation on muscle mass and function with aging: a meta-analysis of randomized controlled trials(). *Prostaglandins Leukot Essent Fatty Acids*. 2021;165:102249. doi:10.1016/j.plefa.2021.102249
14. Huang YH, Chiu WC, Hsu YP, Lo YL, Wang YH. Effects of Omega-3 fatty acids on muscle mass, muscle strength and muscle performance among the elderly: a meta-analysis. *Nutrients*. 2020;12(12):3739. doi:10.3390/nu12123739
15. Bischoff-Ferrari HA, Molino CD, Rival S, et al. DO-HEALTH: vitamin D3-Omega-3-home exercise-healthy aging and longevity trial-design of a multinational clinical trial on healthy aging among European seniors. *Contemp Clin Trials*. 2021;100:106124. doi:10.1016/j.cct.2020.106124
16. Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al. Effect of vitamin D supplementation, Omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA*. 2020;324(18):1855-1868. doi:10.1001/jama.2020.16909
17. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(4):601. doi:10.1093/ageing/afz046
18. Patel SM, Duchowny KA, Kiel DP, et al. Sarcopenia definition & outcomes consortium defined low grip strength in two cross-sectional, population-based cohorts. *J Am Geriatr Soc*. 2020;68(7):1438-1444. doi:10.1111/jgs.16419
19. Gagesch M, Wieczorek M, Abderhalden LA, et al. Grip strength cut-points from the Swiss DO-HEALTH population. *Eur Rev Aging Phys Act*. 2023;20(1):13. doi:10.1186/s11556-023-00323-6
20. Mattle M, Meyer U, Lang W, et al. Prevalence of physical activity and sedentary behavior patterns in generally healthy European adults aged 70 years and older-baseline results from the DO-HEALTH clinical trial. *Front Public Health*. 2022;10:810725. doi:10.3389/fpubh.2022.81072
21. Eckstrom E, Neukam S, Kalin L, Wright J. Physical activity and healthy aging. *Clin Geriatr Med*. 2020;36(4):671-683. doi:10.1016/j.cger.2020.06.009
22. Bislev LS, Grove-Laugesen D, Rejnmark L. Vitamin D and muscle health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Bone Miner Res*. 2021;36(9):1651-1660. doi:10.1002/jbmr.4412
23. LeBoff MS, Murata EM, Cook NR, et al. VITamin D and OmegA-3 TriaL (VITAL): effects of vitamin D supplements on risk of falls in the US population. *J Clin Endocrinol Metab*. 2020;105(9):2929-2938. doi:10.1210/clinem/dgaa311
24. Bischoff-Ferrari HA, Freystatter G, Vellas B, et al. Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. *Am J Clin Nutr*. 2022;115(5):1311-1321. doi:10.1093/ajcn/nqac022
25. LeBoff MS, Bischoff-Ferrari HA. The effects of vitamin D supplementation on musculoskeletal health: the VITAL and

DO-health trials. *J Gerontol A Biol Sci Med Sci*. 2023;78(Supplement_1):73-78:73-78. doi:10.1093/gerona/glad073
26. Bhasin S, Travison TG, Manini TM, et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. *J Am Geriatr Soc*. 2020;68(7):1410-1418. doi:10.1111/jgs.16372
27. Chan R, Leung J, Woo J. A prospective cohort study to examine the association between dietary patterns and sarcopenia in Chinese community-dwelling older people in Hong Kong. *J Am Med Dir Assoc*. 2016;17(4):336-342. doi:10.1016/j.jamda.2015.12.004
28. Conzade R, Grill E, Bischoff-Ferrari HA, et al. Vitamin D in relation to incident sarcopenia and changes in muscle parameters among older adults: the KORA-age study. *Calcif Tissue Int*. 2019;105(2):173-182. doi:10.1007/s00223-019-00558-5
29. Hirani V, Naganathan V, Blyth F, et al. Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: the Concord health and ageing in men project. *Age Ageing*. 2017;46(3):413-420. doi:10.1093/ageing/afw214
30. Vlietstra L, Kirk B, Duque G, et al. Using minimal clinically important differences to measure long-term transitions of osteosarcopenia: the New Mexico aging process study. *Exp Gerontol*. 2023;173:112106. doi:10.1016/j.exger.2023.112106
31. Riuzzi F, Sorci G, Arcuri C, et al. Cellular and molecular mechanisms of sarcopenia: the S100B perspective. *J Cachexia Sarcopenia Muscle*. 2018;9(7):1255-1268. doi:10.1002/jcsm.12363
32. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet*. 2019;393(10191):2636-2646. doi:10.1016/S0140-6736(19)31138-9

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure S1. Flowchart according to CONSORT.
Table S1. Baseline table of the overall sample ($n = 1940$) for the outcome of incident sarcopenia.
Table S2. Treatment effects on the odds of incident sarcopenia based on SDOC over follow-up in the overall sample ($n = 194$).

How to cite this article: Eggimann AK, de Godoi Rezende Costa Molino C, Freystaetter G, et al. Effect of vitamin D, omega-3 supplementation, or a home exercise program on muscle mass and sarcopenia: DO-HEALTH trial. *J Am Geriatr Soc*. 2025;73(4):1049-1059. doi:10.1111/jgs.19266