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Centre on Aging and Mobility

DO HEALTH

Effect of Vitamin D3, omega-3 fatty acids and a simple home exercise program on incident vertebral fractures (VF): results from the DO-HEALTH trial

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Background

- Most promising non-pharmacological strategies to reduce fracture risk in older adults: dietary chances (e.g., vitamin D, omega-3s), exercise
- Mechanistic effects on fracture risk
  - Vitamin D: role in calcium and phosphorus homeostasis, regulation of parathyroid hormone and bone turnover
  - Omega-3s: regulation of vitamin D-dependent calcium absorption, anti-inflammatory pathways
  - Exercise: mechanical loading, mechano-transduction, reduced fall risk
- Existing evidence does not support benefit of Vitamin D for vertebral fracture (VF) risk reduction [1,2,3]
- No data on the effect of omega-3s supplementation on VF risk
- Exercise reduces overall and vertebral fracture risk[4]
- Combined effects of vitamin D, omega-3s and exercise has not been examined

Objectives

To examine the effect of vitamin D3, omega-3s, or a strength-training home exercise program (SHEP), alone or in combination on incident vertebral fractures among generally healthy, community-dwelling older adults.

Methods [5]

Study design

- DO-HEALTH: multi-center, double-blind, 2×2×2 factorial design, RCT
- Data from 4 out of 7 study centers equipped with DXA machines (Zurich, Berlin, Toulouse, Coimbra)

Inclusion criteria

- Community-dwelling adults ≥ 70 years
- Sufficiently mobile to come to study center
- Willing to limit supplementation to ≤ 500 mg calcium/day, ≤ 800 IU vitamin D/day

Exclusion criteria

- Major health events during 5 years prior to enrolment (e.g., myocardial infarction, cancer)
- Intake of active vitamin D metabolites, PTH, calcitonin
- Hypo- and hyperparathyroidism, Paget's disease, epilepsy

Interventions

- Vitamin D3: 2000 IU/day (cholecalciferol) vs. placebo
- Omega-3s: 1 g/day marine omega-3s (EPA:DHA ratio 1:2) vs. placebo
- Exercise: SHEP: five bodyweight and resistance band exercises (3 x 30 min per week) versus control exercise (flexibility)

Assessments

- Four clinical visits: baseline, 12, 24 and 36 months
- Lateral thoracolumbar spine DXA (Lunar iDXA, GE Healthcare)

Assessment

- Semi-automated morphometry analysis (encore software, v13.60.033)
- Classification of etiology (e.g., osteoporotic, degenerative) by radiologist [6]
- Grading of VF severity using the Genant method [7]

Statistical analysis

- Outcome: total number of incident VF over the 36-month follow (including new and progressed VF)
- Negative binominal regression models
- To determine whether treatment effects were additive, 3- and 2-way interaction effects were examined first. If no treatment interactions, main effects were presented
- Adjustments: age, linear spline age at 85 years, sex, BMI, prior fall, study site, offset of the logarithm of time in the study
- Sensitivity analysis: new VF only (excluding progressed VF), progressed VF only (excluding new)
- Subgroup analysis by sex (women, men) and age group (70-74 yrs, ≥ 75 yrs) if interaction terms suggested significant effect modification (*P* value <0.05)

Results

Table 1. *Characteristics of study participants at baseline*

Characteristics	Overall sample (N = 1488)
Age [yrs], mean (SD)	74.9 (4.4)
Women, n (%)	939 (63.1)
Femoral neck T-score, mean (SD)	-1.4 (1.0)
Bone status based on femoral neck T-score	
Low bone mass (osteopenia), n (%)	816 (56.7)
Osteoporosis, n (%)	178 (12.4)
Vitamin D deficiency (< 20 ng/mL), n (%)	646 (43.8)
Physically active ≥ 1/wk, n (%)	1200 (80.7)

Total number of VF

- No treatment interactions → additive treatment effects
- Main results: no significant treatment effects (Figure 1)
- Subgroup results: interaction between sex and SHEP (*P* = 0.03) but no significant treatment effects in subgroups of women (IR = 0.54, 95% CI 0.28, 1.02) and men (IR = 2.27, 95% CI 0.81, 6.38).

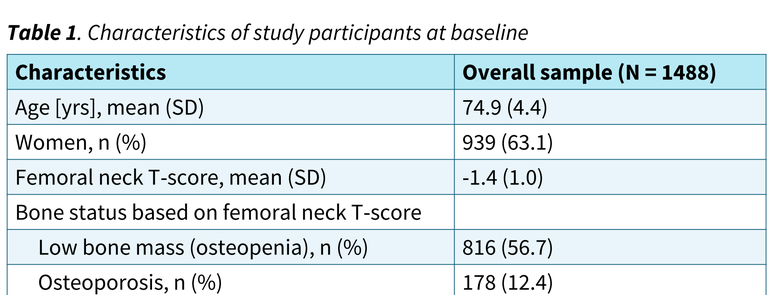

Figure 1. *Treatment effects on total number of VF. Analyses adjusted for age, linear spline at age 85 years, sex, prior fall, BMI, and study site. N = 1369*

Sensitivity analysis for new VF only

- No treatment interactions → additive treatment effects
- Main results: no significant treatment effects
- Subgroups: no significant interactions

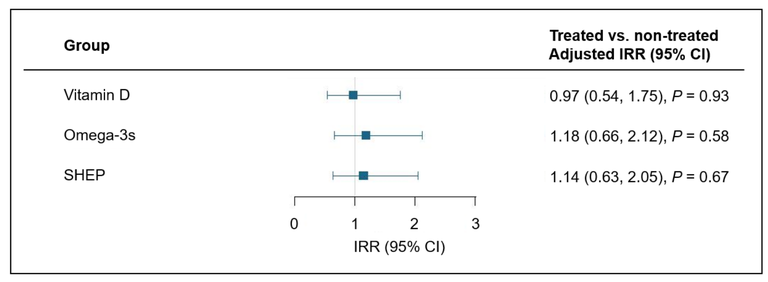

Figure 2. *Treatment effects on number of new VF. Analyses adjusted for age, linear spline at age 85 years, sex, prior fall, BMI, and study site. N = 1369*

Sensitivity analysis for progressed VF only

- No treatment interactions → additive treatment effects
- Main results: SHEP significantly reduced the number of VF progressions (IRR = 0.34, 95% CI 0.16, 0.72).

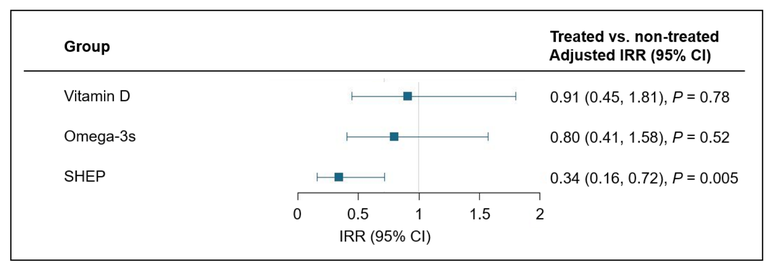

Figure 3. *Treatment effects on number of progressed VF. Analyses adjusted for age, linear spline at age 85 years, sex, prior fall, BMI, and study site. N = 157*

Conclusions

- Among generally healthy and active older adults, daily vitamin D3 and/or omega-3s supplementation did not reduce the rate of incident VF.
- The simple home exercise program did not reduce the total rate of incident VF, but reduced the rate of VF progressions.
- Exercise may exert beneficial effects for secondary prevention of VF, however, the sample size in the sensitivity analyses for VF progressions was small.

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