ABSTRACT NUMBER: 0957

Vitamin D and Marine n-3 Fatty Acid Supplementation and Prevention of Autoimmune Disease in the VITAL Randomized Controlled Trial

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SESSION INFORMATION

Date: Sunday, November 7, 2021

Session Type: Plenary Session

Session Title: Plenary II (0956–0961)

Session Time: 10:45AM-11:00AM

Background/Purpose: In observational studies, vitamin D has been inconsistently associated with reduced risk of several autoimmune diseases, and a large randomized, controlled trial has been lacking. Dietary marine-derived long-chain omega-3 (n−3) fatty acids decrease systemic inflammation and ameliorate symptoms in some autoimmune diseases, but no trials have tested whether supplementation lowers risk of developing autoimmune disease. We tested both vitamin D_3 and n-3 fatty acids for the prevention of autoimmune disease within a large nationwide randomized, controlled trial.

Methods: **VIT**amin D and Omeg**A**-3 Tria**L** (**VITAL**), a U.S. nationwide randomized, double-blind, placebo-controlled trial, enrolled men at least 50 years and women at least 55 years of age in a two-by-two factorial design. Randomization to vitamin D_3 (2000 IU/d) and/or n-3 fatty acids (1000 mg/d) or placebo occurred from November 2011 to March 2014, and treatment continued through December 2017. (VITAL parent trial for cancer and cardiovascular disease prevention was reported in *NEJM*, January 3, 2019). We tested effects of vitamin D_3 and n-3 fatty acids upon autoimmune disease incidence. Incident doctor-diagnosed autoimmune diseases were reported by participants annually and confirmed by medical record review by expert physicians for classification criteria (if existing). The primary endpoint was total incident autoimmune diseases, including rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and all others. Pre-specified secondary endpoints included individual most common autoimmune diseases; and probable autoimmune disease (evidence of incident autoimmune disease but lacking enough medical record data to confirm). Results were displayed in cumulative incidence curves and Cox regression models calculated hazard ratios (HR) of incident autoimmune diseases.

Results: 25,871 participants were randomized: 71% self-reported non-Hispanic Whites, 20% Black, and 9% other racial/ethnic groups, 51% women, mean age 67.1 years. During median follow-up of 5.3 years, confirmed autoimmune disease was diagnosed in 117 participants in the vitamin D_3 group and 155 in the placebo group (HR 0.78, 95% confidence interval 0.61-1.00, p=0.04). Excluding the first 2

years in pre-specified analyses of the primary endpoint, the HR for vitamin D_3 was 0.61 (0.43 – 0.86; 137 cases). Confirmed autoimmune disease was diagnosed in 123 participants in the n-3 fatty acids group and 144 in the placebo group (HR 0.85 (0.67-1.09). Excluding the first 2 years, the HR for the primary endpoint was 0.90 (0.64-1.26). (**Table 1**) When analyzed by factorial design subgroups, HRs for all three active arms vs. placebo/placebo were reduced by 25-30% (**Figures 1-2**). The number needed to treat with both agents for 5 years to prevent one autoimmune disease was 167 (94-769).

Conclusion: Supplementation for 5 years with vitamin D_3 and/or n-3 fatty acids reduced incident autoimmune disease by 25-30% in older adults vs. those who received neither supplement. The effect of vitamin D_3 appeared stronger after 2 years of supplementation.

Figure 1. Incident Autoimmune Disease in the Four Arms of VITAL,over 5.3 years Mean Follow-up, including Confirmed Cases

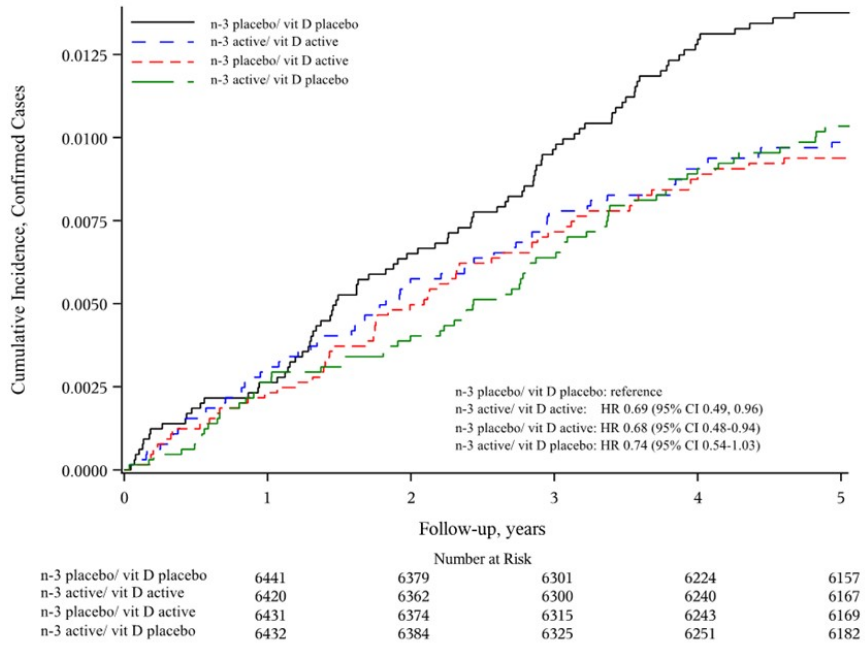

Figure 1.Incident Autoimmune Disease in the Four Arms of VITAL over 5.3 years Mean Follow-up, including Confirmed Cases

Figure 2. Incident Autoimmune Disease in the Four Arms of VITAL, over 5.3 years Mean Follow-up, including Confirmed and Probable Cases

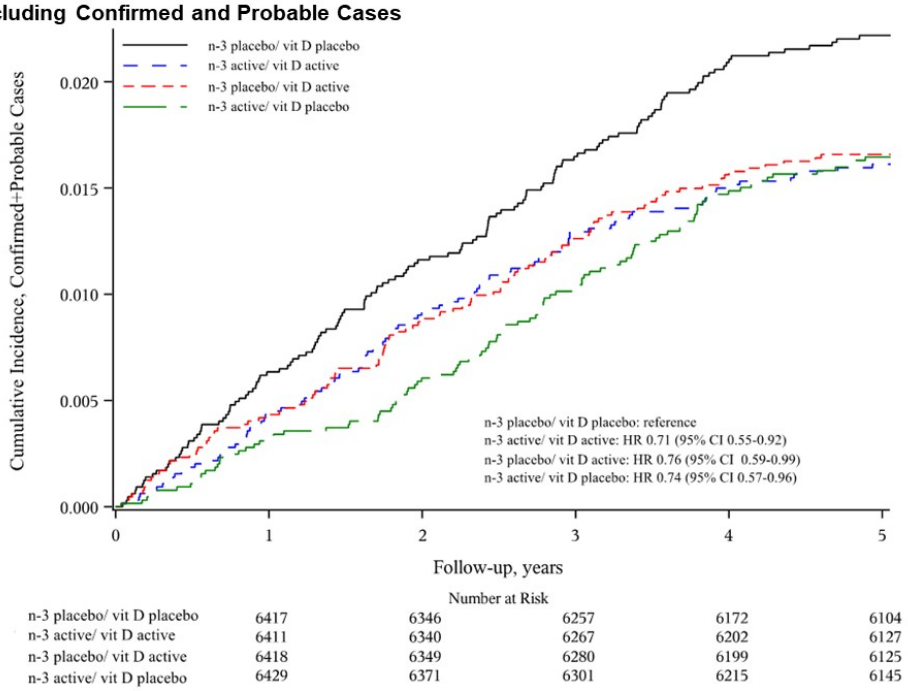

Figure 2. Incident Autoimmune Disease in the Four Arms of VITAL over 5.3 years Mean Follow-up, including Confirmed and Probable Cases

Table 1A. Hazard Ratios and 95% Confidence Intervals (95% CI) for the Primary and Secondary Endpoints, according to Randomized Assignment to Vitamin D_3 or Placebo[a]

Endpoint	Vitamin D_3	Placebo	Hazard Ratio	p value
	(N=12,927)	(N=12,944)	(95% CI)	
	Number of participants with event			
Primary Endpoint				
Confirmed autoimmune diseases	117	150	0.78 (0.61-1.00)	0.04
Secondary Endpoints				
Confirmed+probable autoimmune diseases	199	235	0.85 (0.70-1.02)	0.09
Analyses excluding all pre-randomization AD				
Confirmed autoimmune diseases	98	123	0.79 (0.61-1.03)	0.08
Confirmed+probable autoimmune diseases	161	197	0.81 (0.66-1.00)	0.05
Analyses excluding the first 2 years of follow-up				
Confirmed autoimmune diseases	52	85	0.61 (0.43-0.86)	0.005
Confirmed+probable autoimmune diseases	90	130	0.69 (0.53-0.91)	0.007
Individual autoimmune diseases				
Confirmed rheumatoid arthritis	14	24	0.58 (0.30-1.13)	0.11
Confirmed+probable rheumatoid arthritis	17	27	0.63 (0.34-1.16)	0.14
Confirmed polymyalgia rheumatica[b]	30	43	0.70 (0.44-1.12)	0.14
Confirmed+probable polymyalgia rheumatica	31	43	0.72 (0.46-1.15)	0.17
Confirmed autoimmune thyroid disease	18	11	1.63 (0.77-3.45)	0.20
Confirmed+ probable autoimmune thyroid disease	92	87	1.05 (0.78-1.41)	0.74
Confirmed psoriasis[c]	15	21	0.72 (0.37-1.39)	0.32
Confirmed+probable psoriasis	16	23	0.70 (0.37-1.32)	0.27
Confirmed other autoimmune disease	39	53	0.74 (0.49-1.12)	0.15
Confirmed+probable other autoimmune disease	44	60	0.73 (0.50-1.08)	0.12

Table 1B. Hazard Ratios and 95% Confidence Intervals for the Primary and Secondary Endpoints, according to Randomized Assignment to N-3 Fatty Acids or Placebo[a]

Endpoints	N-3 Fatty Acids	Placebo	Hazard Ratio	p-value
	(N=12,933)	(N=12,938)	(95% CI)	
	Number of participants with event			
Primary Endpoint				
Confirmed autoimmune disease	123	144	0.85 (0.67-1.09)	0.20
Secondary Endpoints				
Confirmed+probable autoimmune disease	196	238	0.82 (0.68-0.99)	0.04
Analyses excluding all pre-randomization autoimmune disease				
Confirmed autoimmune disease	111	119	0.91 (0.70-1.18)	0.48
Confirmed+probable autoimmune disease	180	199	0.90 (0.73-1.10)	0.30
Analyses excluding the first 2 years of follow-up				
Confirmed autoimmune disease	67	74	0.90 (0.64-1.26)	0.54
Confirmed+probable autoimmune disease	110	117	0.94 (0.72-1.23)	0.66
Individual autoimmune diseases				
Confirmed rheumatoid arthritis	14	24	0.58 (0.30-1.13)	0.11
Confirmed+probable rheumatoid arthritis	16	28	0.57 (0.31-1.06)	0.07
Confirmed polymyalgia rheumatica[b]	34	39	0.87 (0.55-1.38)	0.55
Confirmed+probable polymyalgia rheumatica	34	40	0.85 (0.54-1.34)	0.48
Confirmed autoimmune thyroid disease	10	19	0.53 (0.25-1.14)	0.10
Confirmed+ probable autoimmune thyroid disease	79	100	0.80 (0.59-1.07)	0.13
Confirmed psoriasis[c]	22	14	1.57 (0.81-3.07)	0.18
Confirmed+probable psoriasis	23	16	1.44 (0.76-2.72)	0.26
Confirmed other autoimmune disease	42	50	0.84 (0.56-1.26)	0.40
Confirmed+probable other autoimmune disease	45	59	0.76 (0.52-1.12)	0.17

[a]Analyses from Cox regression models controlled for age, sex, race, and other (n-3 fatty acid or vitamin D_3) randomization group
[b]14 confirmed cases of PMR without giant cell arteritis (GCA), 18 confirmed GCA without PMR, and 2 confirmed cases with both
[c]No cases of psoriatic arthritis

Table 1. Hazard Ratios and 95% Confidence Intervals for the Primary and Secondary Endpoints, according to Randomized Assignment to (A) Vitamin D3 or Placebo or (B) N_3 Fatty Acids or Placebo

Disclosures: J. Hahn, None; **N. Cook**, None; **E. Alexander**, None; **S. Friedman**, None; **V. Bubes**, None; **J. Walter**, None; **G. Kotler**, None; **I. Lee**, None; **J. Manson**, None; **K. Costenbader**, Neutrolis, 1, Merck, Exagen, Gilead, 5, Astra Zeneca, Neutrolis, 2.

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