The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL):
Design and Results of a Large Pragmatic Trial

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Grand Rounds: NIH HCS Collaboratory and PCORnet
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ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

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Disclosures

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- **National Cancer Institute and National Heart, Lung and Blood Institute (co-sponsors)**
- **Additional NIH support: ODS, NINDS, and NCCIH (and ancillary study support from multiple institutes)**

Pharmavite of Northridge, CA (vitamin D) and Pronova BioPharma of Norway and BASF (Omacor fish oil, known as Lovaza in the U.S.) donated study pills, matching placebos, and calendar packaging.

Quest Diagnostics (San Juan Capistrano, CA) measured serum 25OHD and other biomarkers at no cost.

Objectives

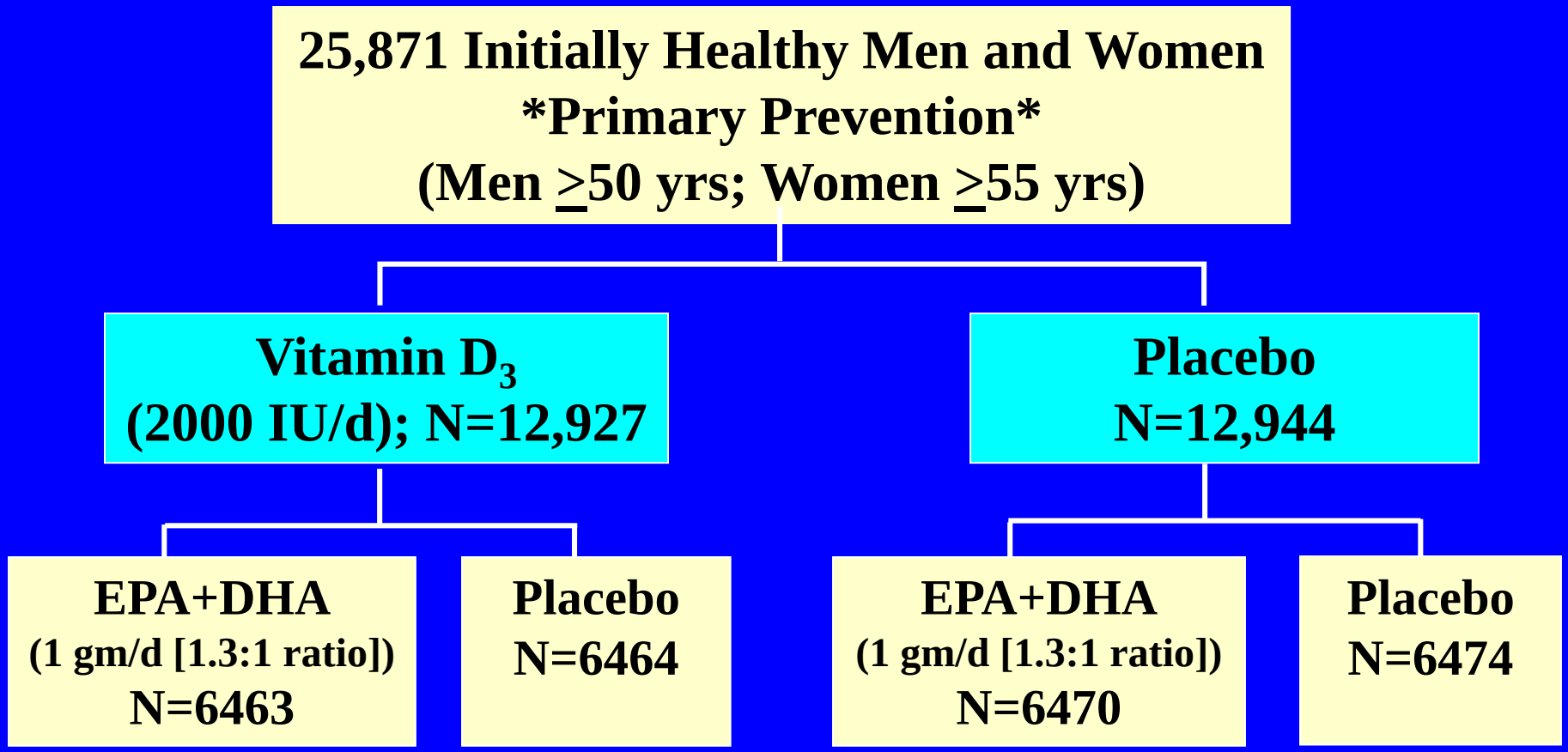
- **Review the rationale and design of a large-scale randomized trial of vitamin D and marine omega-3 supplements in the primary prevention of CVD and cancer.**
- **Summarize design features facilitating recruitment, retention, rigor, and cost-efficiency of a large pragmatic trial.**
- **Describe the trial's findings for each supplement in relation to CVD and cancer outcomes.**

Large, Simple, Mail-based Randomized Clinical Trials

Trial Name	Intervention Tested (factorial design vs placebo)
Physicians' Health Study I	Aspirin, beta-carotene
Physicians' Health Study II	Multivitamins, vitamin E, vitamin C
Women's Health Study	Aspirin, vitamin E
Women's Antioxidant and Folic Acid Study	Beta carotene, vitamin C, vitamin E, folic acid/B6/B12
*VIT*amin D and Omeg*A*-3 Tria*L* (VITA*L*)	Vitamin D, omega-3 fatty acids

Highly cost-effective nation-wide recruitment: ~$100-200/participant/year in direct costs.

The VITamin D and OmegA-3 TriaL (VITAL): Design



Median Treatment Period = 5.3 years.

5,106 African Americans.

Blood collection in ~16,953 at baseline, follow-up bloods in ~6000.

Adapted from: Manson JE, Bassuk SS, Lee I-M, et al. *Cont Clinical Trials*, 2011.

Rationale for *VITAL*

- **Emerging evidence that vitamin D and marine omega-3s (EPA+DHA) reduce risk of cancer and CVD.**
- **Growing use of these supplements underscores the need for conclusive evidence on benefits and risks.**
- **No previous large-scale randomized clinical trials of these agents in the primary prevention of cancer and CVD had been conducted.**

VITAL Specific Aims

Primary Aims

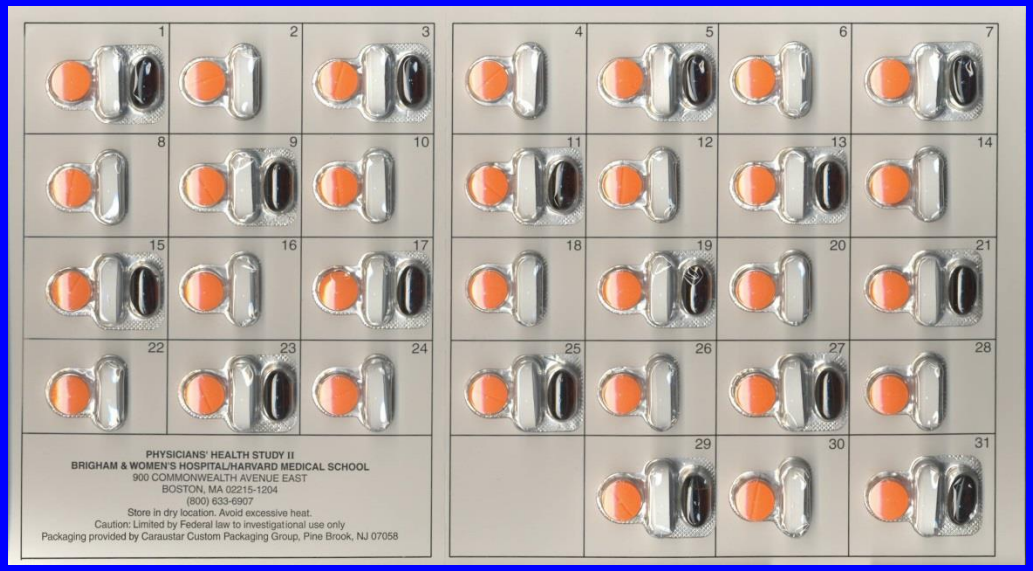
1) To test whether vitamin D_3 and/or omega-3 fatty acids reduce risk of (a) major CVD events (composite of MI, stroke, CVD death), (b) total invasive cancer.

Secondary Aims

1) To test whether these agents lower risk of (a) MI/stroke/CVD death/PCI/CABG and (b) individual components of primary CVD outcome.
2) To test whether these agents lower risk of (a) site-specific cancer, (b) total cancer mortality.
3) Assess key subgroups, including age, sex, race/ethnicity, nutrient status at baseline.

Monthly Calendar Packs

Physicians' Health Study II



VITAL

Baseline Characteristics of the 25,871 VITAL Participants

N	25,871
Mean age ± SD, years	67.1 ± 7.1
Sex, % female	13,085 (50.6)
Race/ethnicity, %	
Non-Hispanic White	18,046 (71.3)
African American	5,106 (20.2)
Hispanic (not African American)	1,013 (4.0)
Asian/Pacific Islander	388 (1.5)
American Indian/Alaskan Native	228 (0.9)
Mean body mass index (kg/m^2) ± SD	28.1 (5.7)
Current smoking, %	1,836 (7.2)
Hypertension, treated, %	12,791 (49.8)
High cholesterol, treated, %	9,524 (37.5)
Diabetes, %	3,549 (13.7)

VITAL Recruitment Strategies

Overall

- Population-based (nationwide) and targeted mailings
- Media reports on VITAL (with mention of website and 1-800 number for sign up)
- Advertising (radio, print)
- Study-related brochures in medical clinics/health centers

Targeted Efforts to Enhance Minority Recruitment

- Targeted minority-enriched mailings, including alumni/ae of historically black colleges and universities
- Community health centers
- Church bulletins
- Collaborations with investigators on recruitment in large urban areas (Chicago)

Ancillary Studies in VITAL

- Cognitive Function
- Diabetes/Glucose Tolerance
- Hypertension
- Autoimmune Disorders
- Asthma/Respiratory Diseases
- Fractures
- DXA/Bone Microarchitecture
- Diabetic Nephropathy
- Mood Disorders/Depression
- Infections
- 2D Echocardiogram
- Macular Degeneration
- Anemia
- Atrial Fibrillation
- Mammographic Density

In-clinic visits
(in subset)

Hybrid Design In-Clinic Visits: Protocol (Baseline and 2 Yrs)

- Blood pressure measurements
- Height, weight, waist, other anthropometrics
- Urine collection
- OGTT (2-hr) and fasting blood collections
- Spirometry
- Physical performance/strength/frailty
- Cognitive function/mood/depression
- ECG and 2D Echocardiogram
- DXA scans, bone microarchitecture imaging

VITAL Retention Strategies

- Participant newsletters
- Study website: posted videos, articles, media reports
- Birthday and New Year's cards
- Incentive gifts (penlight, magnifiers, calendars, etc.)
- Honoraria for participation in in-clinic visits, repeat blood collections, etc.
- Others

Cost-Efficiency Measures

- **Hybrid design, predominantly mail-based.**
- **Factorial design (2 interventions simultaneously).**
- **Blood-collections at baseline and follow-up (EMSI or Quest).**
- **Donation of study pills and calendar packaging by industry.**
- **Collaboration with Quest and Atherotech laboratories to conduct multiple lab assays.**
- **Multiple ancillary studies that leverage the VITAL infrastructure.**

(Direct costs <$140 per participant per year, <$70 per agent tested.)

Follow-up Rates and Treatment Compliance

- **Mean follow-up rates over 5.3 yrs:**

  Morbidity (>93%); mortality (>98%).

- **Study pill adherence:**

  Mean of >83% over 5.3-yr follow-up.

High adherence supported by biomarker studies at baseline and 1 year (n ~1,600):

- **Plasma omega-3 index: ↑54.7% with n-3s vs <2% with placebo.**
- **Serum 25(OH)D: ↑40% with vitamin D vs ~2% with placebo.**

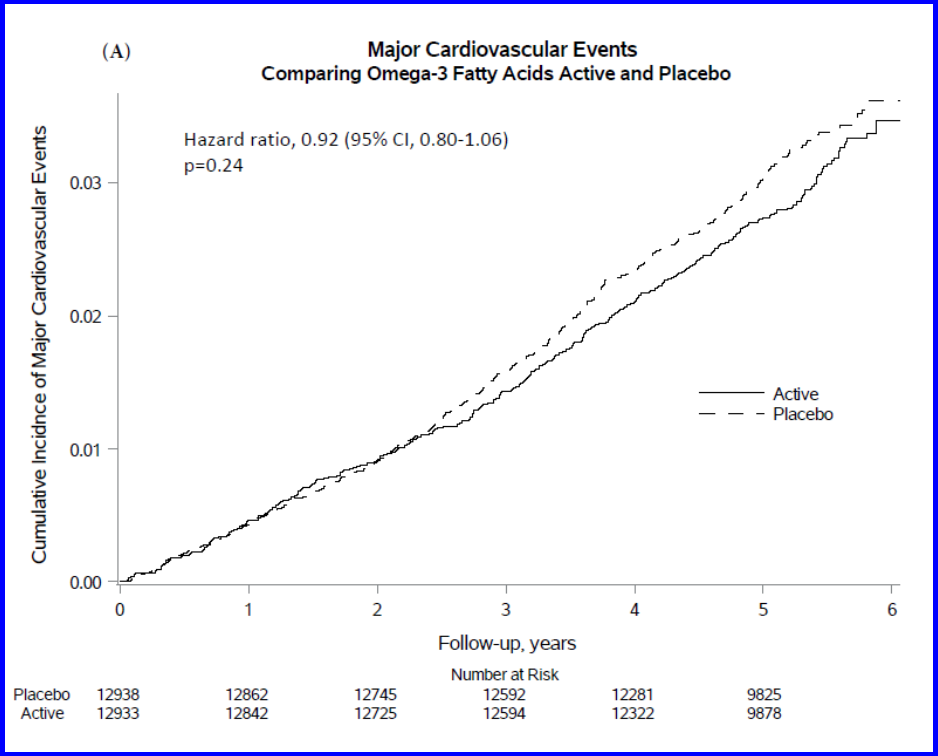
Hazard Ratios (HR) and 95% CIs of the CVD Outcomes by Randomized Assignment to Omega-3 Fatty Acids

	Omega-3s (N=12,933)	Placebo (N=12,938)	HR	(95% CI)
	No. of Events			
Cardiovascular disease (1°and 2° outcomes)				
Major CVD events[a]	386	419	0.92	(0.80-1.06)
Total MI	145	200	0.72	(0.59-0.90)*
Total stroke	148	142	1.04	(0.83-1.31)
CVD mortality	142	148	0.96	(0.76-1.21)
Major CVD + PCI/CABG[b]	527	567	0.93	(0.82-1.04)
Other vascular outcomes[c]				
PCI	162	208	0.78	(0.63-0.95)*
CABG	85	86	0.99	(0.73-1.33)
Fatal MI	13	26	0.50	(0.26-0.97)*
CHD death	37	49	0.76	(0.49-1.16)
Total CHD[d]	308	370	0.83	(0.71-0.97)*

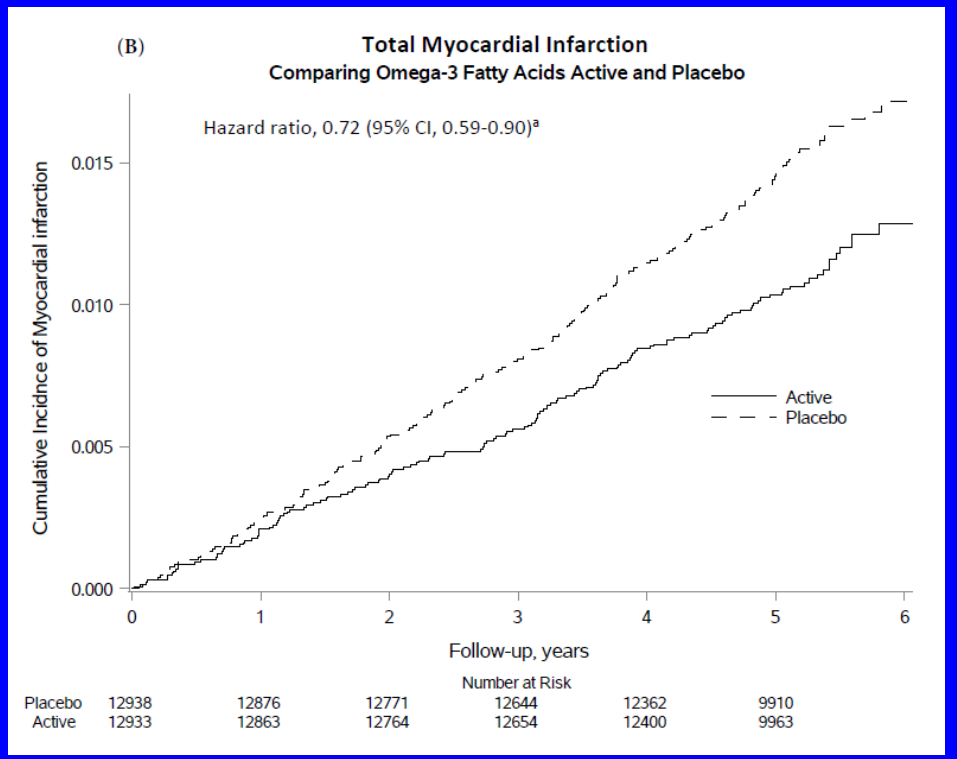
[a]Primary outcome. A composite of MI, stroke and CVD mortality. [b]Expanded CVD composite
[c]Not prespecified as primary or secondary outcomes. [d]A composite of MI, PCI/CABG, and CHD death.
All analyses are intention-to-treat. *Nominal p-value <0.05. For MI, the nominal p-value was 0.003.

Cumulative Incidence Rates of Major CVD Events and Total MI by Year of Follow-up: Omega-3s vs. Placebo

Major CVD Events



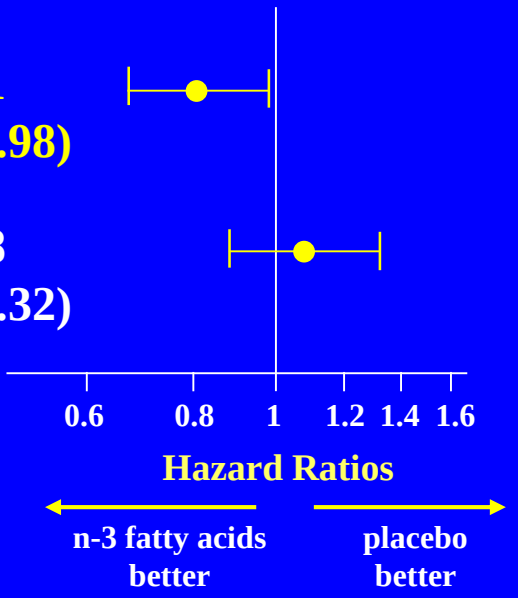
Total MI



For major CVD events: p-value = 0.24
For total MI: nominal p-value = 0.003 and Bonferroni-adjusted p-value = 0.015.

Hazard Ratios of Major CVD Events by Baseline Fish Consumption, Comparing Omega-3 Fatty Acids and Placebo Groups

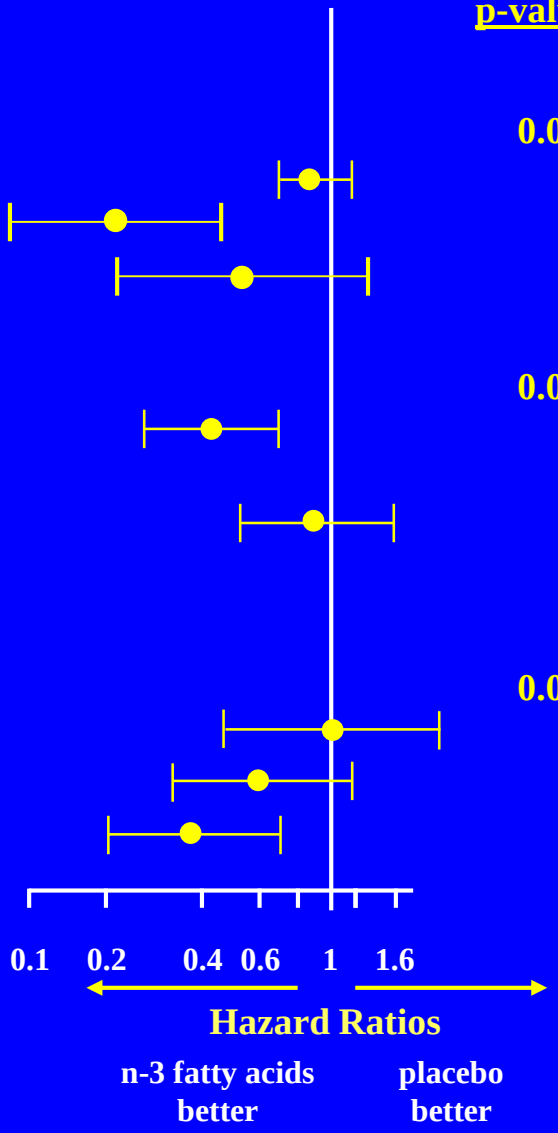
Subgroups	Total	Omega-3s	Placebo	HR (95% CI)	Interaction p-value
		No. of Events			
Fish Consumption (servings/wk)	25,435				0.045
<median (1.5 servings/wk)	13,514	189	232	0.81 (0.67-0.98)	
≥median (1.5 servings/wk)	11,921	189	176	1.08 (0.88-1.32)	



Source: Manson JE, Cook NR, Lee I-M, et al. *NEJM* 2018.

Hazard Ratios of Total MI by Subgroups, Comparing Omega-3 Fatty Acids and Placebo Groups

Subgroups	Total	Omega-3s	Placebo	HR (95% CI)	Interaction p-value
		No. of Events			
Race	25,304				0.001
Non-Hispanic White	18,046	126	135	0.93 (0.73-1.18)	
African American	5,106	9	39	0.23 (0.11-0.47)	
Other	2,152	8	16	0.54 (0.23-1.26)	
Fish Consumption (servings/wk)	25,435				0.048
<median (1.5 servings/wk)	13,514	74	121	0.60 (0.45-0.81)	
≥median (1.5 servings/wk)	11,921	67	72	0.94 (0.67-1.31)	
# of Cardiovascular Risk Factors	25,871				0.047
No risk factors	7,802	41	40	1.01 (0.65-1.56)	
1 risk factor	8,948	53	70	0.75 (0.53-1.08)	
2 or more risk factors	9,121	51	90	0.57 (0.41-0.81)	



Source: Manson JE, Cook NR, Lee I-M, et al. *NEJM* 2018.

Hazard Ratios (HR) and 95% CIs of the CVD Outcomes by Randomized Vitamin D Assignment

	Vitamin D (N=12,927)	Placebo (N=12,944)	HR	(95% CI)
	No. of Events			
Cardiovascular disease (CVD) (1°and 2° outcomes)				
Major CVD events[a]	396	409	0.97	(0.85-1.12)
Total MI	169	176	0.96	(0.78-1.19)
Stroke	141	149	0.95	(0.76-1.20)
CVD mortality	152	138	1.11	(0.88-1.40)
Major CVD + PCI/CABG[b]	536	558	0.96	(0.86-1.08)
Other vascular outcomes[c]				
PCI	182	188	0.97	(0.79-1.19)
CABG	73	98	0.75	(0.55-1.01)
MI death	24	15	1.60	(0.84-3.06)
Stroke death	19	23	0.84	(0.46-1.54)

[a]Primary outcome. A composite of MI, stroke and CVD mortality. [b]Expanded CVD composite.
[c]Not prespecified as primary or secondary outcomes.

Hazard Ratios (HR) and 95% CIs of Major CVD Events Comparing Vitamin D and Placebo Groups, According to Baseline Characteristics (Prespecified Subgroups)

		Major CVD Events			
		No. of Events			Interaction
	Total	Vitamin D	Placebo	(95% CI)	P-value
Baseline Serum 25(OH)D[a]	15,787				0.75
<20 ng/mL (50 nmol/L)	2,001	34	34	1.09 (0.68-1.76)	
≥20 ng/mL (50 nmol/L)	13,786	218	216	1.00 (0.83-1.21)	
Baseline Serum 25(OH)D[a]	15,787				0.42
<cohort median	7,812	128	139	0.94 (0.74-1.20)	
≥cohort median	7,975	124	111	1.09 (0.84-1.41)	
Omega-3 Fatty Acids Randomization Status	25,871				0.56
Placebo group	12,938	210	209	1.01 (0.83-1.22)	
Omega-3 group	12,933	186	200	0.93 (0.76-1.14)	

[a]25(OH)D = 25 hydroxyvitamin D.

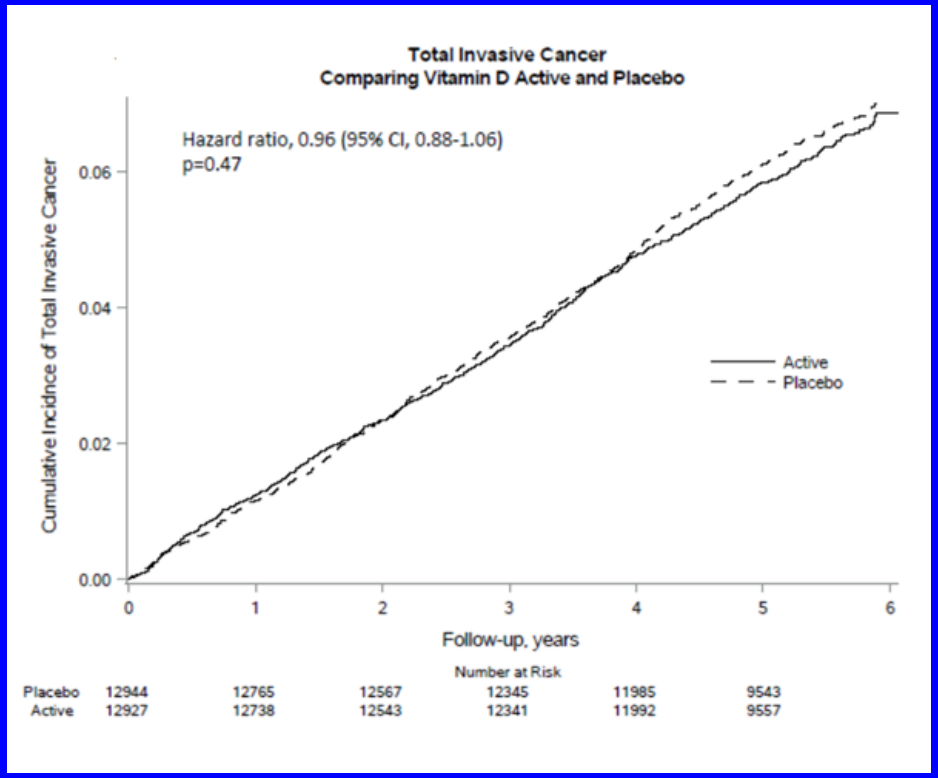
Hazard Ratios (HR) and 95% CIs of the Cancer Endpoints and All-Cause Mortality by Randomized Vitamin D Assignment

	Vitamin D (N=12,927)	Placebo (N=12,944)	HR	(95% CI)
	No. of Events			
Total invasive cancer	793	824	0.96	(0.88-1.06)
Cancer death	154	187	0.83	(0.67-1.02)
All-cause mortality	485	493	0.99	(0.87-1.12)
Excluding the first 2 years of follow up				
Total invasive cancer	490	522	0.94	(0.83-1.06)
Cancer death	112	149	0.75	(0.59-0.96)*
All-cause mortality	368	384	0.96	(0.84-1.11)

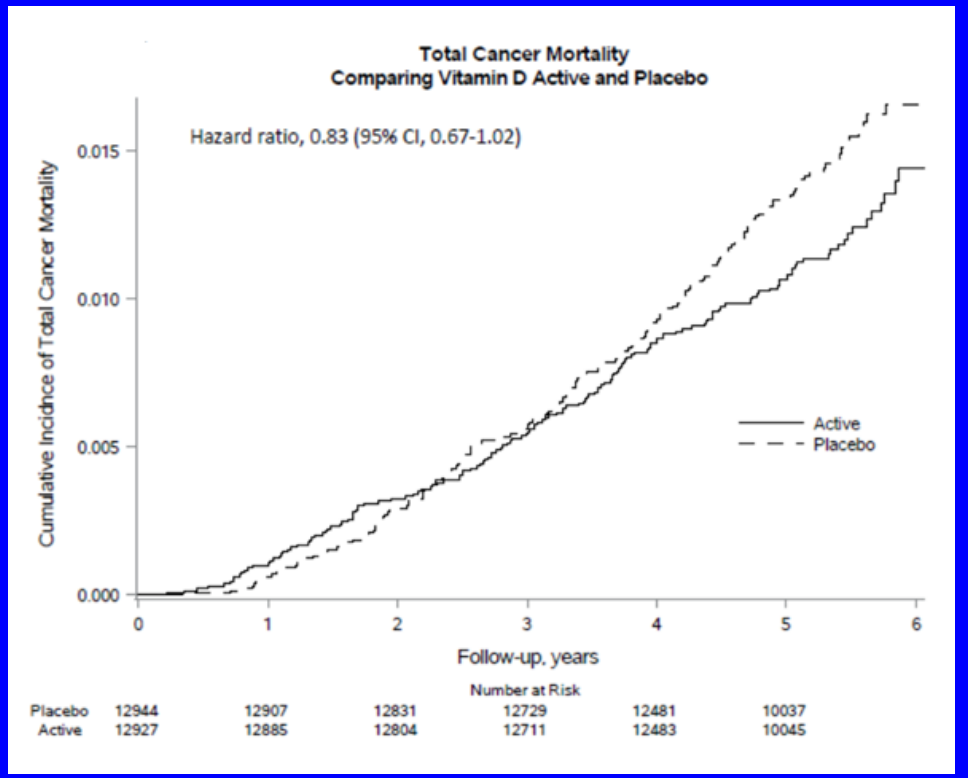
*Nominal p-value = 0.024.

Cumulative Incidence Rates of Total Cancer Incidence and Cancer Mortality by Year of Follow-up: Vitamin D vs. Placebo

Total Cancer Incidence

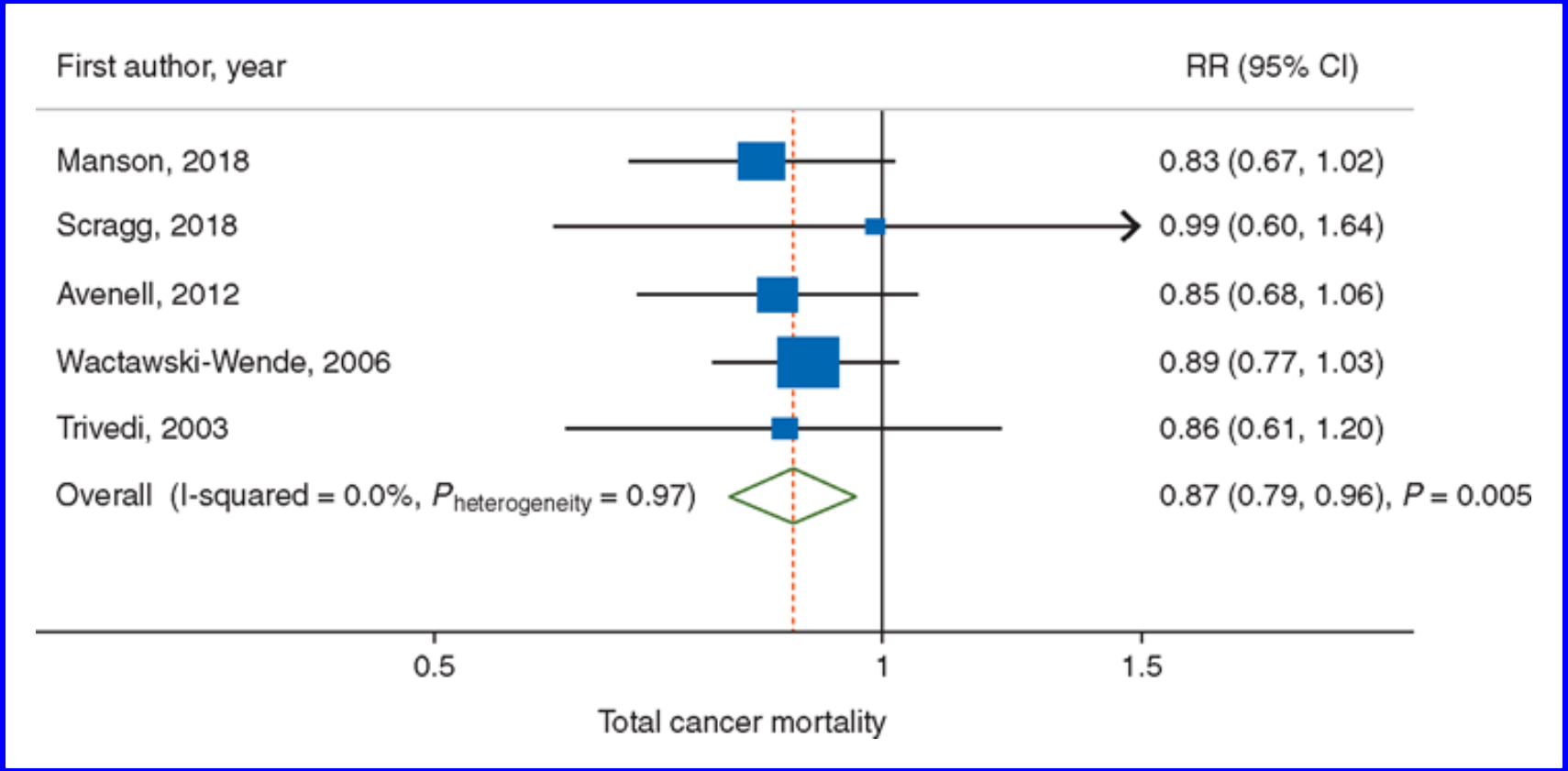


Total Cancer Mortality



Excluding first 2 yrs: Total cancer mortality HR = 0.75 (0.59-0.96); nominal p-value = 0.024.

Updated Meta-Analysis of Randomized Trials of Vitamin D Supplementation and Cancer Mortality



Source: Keum, et al. *Ann Oncol* [e-pub 2/22/19]

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Total Invasive Cancer Comparing Vitamin D and Placebo Groups, According to Prespecified Subgroups

Subgroup	Total N	No. of Events		HR (95% CI)	Interaction P-value
		Vitamin D	Placebo		
Race	25,304				0.085
Non-Hispanic white	18,046	626	632	0.99 (0.89-1.11)	
African American	5,106	98	126	0.77 (0.59-1.01)	
Body Mass Index (kg/m^2)	25,254				0.002
<25	7,843	206	278	0.76 (0.63-0.90)	
25-<30	10,122	338	323	1.04 (0.90-1.21)	
≥30	7,289	228	199	1.13 (0.94-1.37)	
Baseline Serum (25(OH)D	15,787				0.99
<20 ng/mL	2,001	58	63	0.97 (0.68-1.39)	
≥20 ng/mL	13,786	459	464	0.98 (0.86-1.12)	

Intention-to-treat analyses.

Source: Manson JE, Cook NR, Lee I-M, et al. *NEJM* 2018.

Side Effects/Adverse Events

- No significant side effects with either agent.
- No increased risk of hypercalcemia with vitamin D.
- No increased risk of bleeding with omega-3s.
- No increase in GI symptoms with either agent.

Relative safety of both supplements over 5.3 years.

Conclusions

- **Neither omega-3s nor vitamin D significantly reduced the primary endpoints of major CVD events or total invasive cancer.**
- **Omega-3s reduced total MI by 28% (nominal p-value=0.003, Bonferroni-adjusted p-value=0.015), with greatest reductions in those with low dietary fish intake and in African Americans. PCI, fatal MI, total CHD (MI + coronary revasc + CHD death) were also reduced.**
- **Vitamin D reduced total cancer mortality in analyses excluding early follow up.**
- **Next steps: Continued follow-up; completion of ancillary studies (stay tuned!); replication studies.**

Trial Design: Conclusions/Recommendations

- A hybrid design (remote or mail-based intervention plus serial in-clinic visits in a sample) has advantages (quality and cost-efficiency).
- Baseline and follow-up blood/biospecimen collections are important and feasible (EMSI and Quest Center collaborations).
- Both active and passive surveillance of clinical endpoints has advantages and minimizes bias.
- Ancillary studies should be considered early to allow collection of pre-randomization data/measurements/imaging.
- Recruitment of a diverse study population requires resources.

Study website: **www.vitalstudy.org**

VITAL: Future Plans

- Continued follow-up/endpoint confirmation for 5 yrs (to address latency).
- CMS linkage surveillance of the cohort .
- Genetic studies:
  - Targeted gene variants (vitamin D metabolism, absorption, receptor function).
  - Targeted gene variants (n-3 FAs synthesis and activation)
  - Pursue promising signals in the trial (among African Americans, BMI, etc.)
- Gene expression and DNA methylation studies (by race, BMI, baseline nutrient status).
- Other biomarker studies (inflammation; fatty acid profiles, vit K, others).
- Support for infrastructure to continue ongoing ancillary studies
- Foster new ancillary studies (nation-wide collaborations).

Thank you to VITAL Participants, Investigators, and Staff!

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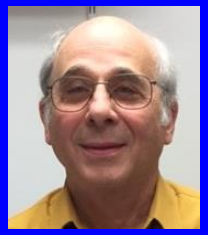
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