

# POEMs

## Patient-Oriented Evidence That Matters

### Vitamin D Is Not Effective as Primary Prevention of Cardiovascular Disease or Cancer

#### Clinical Question

Does vitamin D supplementation prevent cardiovascular events or cancer in patients without known vascular disease or cancer?

#### Bottom Line

Vitamin D supplementation does not prevent cardiovascular events or cancer in mostly nondiabetic adults (men 50 years and older, women 55 years and older). (Level of Evidence = 1b)

#### Synopsis

Vitamin D deficiency is associated with many bad things including cancer, vascular disease, and dementia. This study is the first adequately powered U.S. trial of vitamin D supplementation for primary prevention of cardiovascular disease and cancer. It was designed as a factorial trial, with patients randomized to receive vitamin D 2,000 IU or placebo, and to receive marine n-3 fatty acids (also known as omega-3 fatty acids) or placebo. The marine n-3 fatty acid results are reported separately. The researchers recruited a total of 25,871 men 50 years and older, and women 55 years and older who had no history of cardiovascular disease or cancer. The groups were balanced at the start of the study, with a mean age of 67 years, 51% women, approximately 20% African Americans, and 14% with diabetes

mellitus. Participants began with a three-month placebo run-in period to exclude those who were noncompliant (approximately one-third overall), which could overestimate the potential benefit seen in clinical practice. Of the participants, 12% had a vitamin D level less than 20 ng per mL (50 nmol per L) and 45% had a level less than 30 ng per mL (75 nmol per L). At the end of the median follow-up of 5.3 years, there was no difference in any of the trial end points (i.e., cardiovascular events, cardiovascular deaths, incident cancer, cancer deaths, or all-cause mortality). There was a small reduction in cancer deaths (112 vs. 149; hazard ratio = 0.75; 95% CI, 0.59 to 0.96), but that was only seen in the post hoc analysis that excluded events in the first two years with the rationale that any effect would take time to become apparent. Given the large number of comparisons made (19 in one table alone), this outcome could have occurred by chance. Results were similar for the subgroup of patients with lower vitamin D levels at baseline.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Government

**Allocation:** Concealed

**Setting:** Population-based

**Reference:** Manson JE, Cook NR, Lee IM, et al.; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380(1):33-44.

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### Omega-3 Fatty Acids Do Not Prevent Cancer or Cardiovascular Disease Events

#### Clinical Question

Do marine n-3 fatty acids (also called omega-3 fatty acids) reduce the risk of cardiovascular events or cancer in patients without known vascular disease or cancer?

#### Bottom Line

This is the second large, well-designed study (the first one included patients with diabetes mellitus; this one included patients without diabetes)

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that found no benefit from a 1-g daily dosage of marine n-3 fatty acid supplementation for the primary prevention of cardiovascular disease or cancer. This study featured more than 20 comparisons, so the small reduction found in myocardial infarctions may be due to chance alone. (Level of Evidence = 1b)

### Synopsis

A recent POEM reported that a U.K. trial of marine n-3 fatty acids in 15,000 patients with diabetes found no evidence of benefit as primary prevention of cardiovascular disease or cancer. The current study is the first adequately powered U.S. trial of marine n-3 (omega-3) fatty acids for primary prevention. The researchers recruited a total of 25,871 men 50 years and older and women 55 years and older who had no history of cardiovascular disease or cancer. The groups were balanced at the start of the study, with a mean age of 67 years, 51% women, and 14% with diabetes. The investigators used a three-month placebo run-in period to exclude patients who were noncompliant, which was approximately one-third of those initially recruited. This could overestimate the potential benefit seen in clinical practice. Participants were randomly assigned to a 1-g daily dosage of marine n-3 fatty acids or placebo. The median follow-up was 5.3 years. There was no reduction in the likelihood of cancer diagnosis or the primary composite cardiovascular outcome (i.e., cardiovascular death, nonfatal myocardial infarction, or ischemic stroke). There was no difference between groups regarding cardiovascular or all-cause mortality. There was a reduction in total myocardial infarctions (hazard ratio = 0.72; 95% CI, 0.59 to 0.90), although the absolute reduction was small (145 vs. 200 total myocardial infarctions with more than 12,000 patients in each group). It is important not to make too much of this finding because there were 24 comparisons made in the primary analysis, so this one could be caused by chance alone. There was no difference between groups regarding adverse events. A subgroup analysis found a modest, but statistically significant, reduction in the primary composite outcome for persons who ate fewer than 1.5 servings of fish per week, but not in those who ate more.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Government

**Allocation:** Concealed

**Setting:** Population-based

**Reference:** Manson JE, Cook NR, Lee IM, et al.; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med.* 2019;380(1):23-32.

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## Normal Vital Signs and Pulmonary Examination Results Rule Out CAP in Adults with Acute Respiratory Infection

### Clinical Question

What signs and symptoms are the most useful for excluding the diagnosis of pneumonia in community-dwelling adults with an acute respiratory infection?

### Bottom Line

Community-dwelling adults who present to a primary care office with acute respiratory infection symptoms but normal vital signs and normal findings on a pulmonary examination have only a 0.4% likelihood of community-acquired pneumonia (CAP). (Level of Evidence = 1a)

### Synopsis

Identifying signs and symptoms that reliably rule out CAP may help reduce the overuse of radiography and/or laboratory testing. Investigators systematically searched MEDLINE and reference lists of pertinent articles for studies that used a clinical decision rule to diagnose CAP in the outpatient setting. Eligible criteria included the use of chest radiography or computed tomography as the reference standard for all enrolled patients or a random/systematic sample of the enrolled patients. Only studies that recruited adults or adolescents in an outpatient setting, including the emergency department, were included. Two individuals independently reviewed potential studies for inclusion criteria and methodologic quality using standard criteria. The resolution of any disagreements occurred after consensus discussion with a third reviewer.

A total of 12 studies met inclusion criteria, of which six were performed in an emergency department setting and six in a primary care

setting. Sample sizes ranged from 246 to 2,820 patients. Six studies were found to be at low risk of bias; the remaining six were at moderate risk of bias. The combination of normal vital signs (temperature, respiratory rate, and heart rate) plus normal findings on the pulmonary examination reliably excluded CAP (sensitivity = 0.96; 95% CI, 0.92 to 0.98; negative likelihood ratio = 0.10; 0.07 to 0.13).

**Study design:** Systematic review

**Funding source:** Self-funded or unfunded

**Setting:** Various (meta-analysis)

**Reference:** Marchello CS, Ebell MH, Dale AP, et al. Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: A systematic review and meta-analysis. *J Am Board Fam Med.* 2019;32(2):234-247.

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## Weak Evidence Supports Augmentation Therapy for Treatment-Resistant Depression

### Clinical Question

What is the evidence for augmentation therapy in patients with treatment-resistant depression?

### Bottom Line

There is weak research to guide treatment decisions for patients who have not responded to two adequate courses of antidepressant treatment. One study of cognitive behavior therapy showed benefit over placebo. Aripiprazole (Abilify) had a small effect, but neither antipsychotics nor lithium provided benefit over placebo. (Level of Evidence = 1a)

### Synopsis

The investigators searched two databases (but not Cochrane CENTRAL) to identify randomized controlled trials that investigated the benefit of augmentation therapy in patients with depression despite two attempts at treatment of adequate duration. The authors followed PRISMA guidelines for conducting systematic reviews. They identified 28 studies. Twenty-five investigated additional pharmacotherapy and three investigated psychological therapies. The studies were of moderate to high quality. There was considerable heterogeneity across the study results attributed to different treatments, duration of study, and study quality. Cognitive behavior therapy was more effective than placebo in a single study, but other counseling interventions were not. Treatment with antipsychotics or lithium was not more effective than placebo. Aripiprazole had a small likelihood of producing benefit (effect size 1.33; 95% CI, 1.23 to 1.44).

**Study design:** Meta-analysis (randomized controlled trials)

**Funding source:** Government

**Setting:** Various (meta-analysis)

**Reference:** Strawbridge R, Carter B, Marwood L, et al. Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis. *Br J Psychiatry.* 2019;214(1):42-51.

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**Editor's Note:** Dr. Ebell is Deputy Editor for Evidence-Based Medicine for *AFP* and cofounder and Editor-in-Chief of Essential Evidence Plus, published by Wiley-Blackwell. Dr. Shaughnessy is an Assistant Medical Editor for *AFP*. ■