

Antioxidant Research



What's the Problem?

Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases - PubMed (nih.gov)

Objective: Assess the effects of antioxidant supplements on mortality in adults

Search Methods: Searched various databases for relevant trials up to February 2011

Selection Criteria: Included randomized clinical trials on antioxidants (beta-carotene, vitamins A, C, E, selenium) vs. placebo or no intervention



78 trials with 296,707 participants included

Antioxidants showed no significant effect on mortality in the random-effects model meta-analysis but increased mortality in the fixed-effect model

Fixed-Effect Model: Assumes all studies measure the same thing and any differences between them are due to chance. It calculates a weighted average of the study results, giving more weight to larger studies. Best when all studies are similar.

Random-Effects Model: Allows for the possibility that studies are measuring slightly different things. It considers both chance differences and real differences between studies. It also calculates a weighted average, but it gives more weight to studies with less variability. Best when studies are diverse.

[Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider - PMC \(nih.gov\)](#)

The likelihood of bias in the studies and the specific type of antioxidant being used were significant factors in predicting the variability observed

The presence of bias in the studies and the specific antioxidants being tested had a notable impact on the differences seen among the trial results.

No significant difference between primary and secondary prevention trials



In trials with low risk of bias,
antioxidant supplements significantly
increased mortality

Beta-carotene and vitamin E increased
mortality

Vitamin C and selenium did not
significantly affect mortality

Higher doses of vitamin A associated
with increased mortality



Authors' Conclusions:

No evidence to support antioxidant supplements for prevention. Beta-carotene and vitamin E may increase mortality, as may higher doses of vitamin A. Antioxidant supplements should be considered as medicinal products and undergo further evaluation



[A Systematic Review of Effects of Vitamin E on the Cardiovascular System - PMC \(nih.gov\)](#)

The majority of the papers, including 75% of the total population in this review, suggested no role of vitamin E in preventing CVD and CVD mortality. Some studies also suggested that a high level of vitamin E can be associated with adverse cardiovascular outcomes. Thus, one should be prudent about taking vitamin E supplementation for cardiovascular risk prevention.

[The Safety of Vitamin E Supplements - Canada.ca](#)



Recent studies suggest high-dose vitamin E supplements might not prevent heart disease or cancer and could be harmful

Studies involved specific groups:

People aged 55 or older with heart disease or diabetes

People with cancer or history of cancer

People at higher risk of developing these diseases



One study found an increased risk of heart failure in patients with heart disease or diabetes taking 400 IU of vitamin E daily

Another study showed an increased likelihood of developing additional cancers among cancer patients receiving radiation therapy and taking vitamin E supplements

Studies have limitations and unclear applicability to healthy individuals

More research, especially on the long-term effects, is needed



Vitamin D supplementation for
prevention of mortality in adults -
PubMed (nih.gov)

Background: Previous evidence on vitamin D's effects on mortality was inconclusive. A recent review suggested vitamin D3 might reduce mortality in elderly women

This study updates and reevaluates the benefits and harms of vitamin D supplementation for mortality prevention



Objectives: Evaluate the effects of vitamin D supplementation on mortality in healthy adults and those with stable diseases

Search Methods: Reviewed trials from various databases and sources up to February 2012

Selection Criteria: Included randomized trials comparing any type, dose, duration, and route of vitamin D supplementation with placebo or no intervention in adults



159 trials were identified; 56 trials with 95,286 participants were analyzed for mortality

Most participants were elderly women

Vitamin D3 decreased mortality, while other forms did not

Vitamin D3 reduced cancer mortality, but when combined with calcium, increased the risk of kidney stones



Alfacalcidol (synthetic) and calcitriol increased the risk of high blood calcium levels.

Authors' Conclusions: Vitamin D3 reduced mortality in elderly individuals, while other forms showed no significant benefit.

Vitamin D3 combined with calcium increased kidney stones, and alfacalcidol and calcitriol raised blood calcium levels.

More placebo-controlled trials are needed due to potential biases and weaknesses in the evidence.



Link between high levels of niacin -- a common B vitamin -- and heart disease, study suggests | ScienceDaily

Dr. Stanley Hazen and his team at the Cleveland Clinic uncovered a novel pathway connecting elevated niacin levels to heart disease

Excess niacin prompts the production of 4PY (4PY-R), a harmful compound that sparks vascular inflammation and exacerbates atherosclerosis

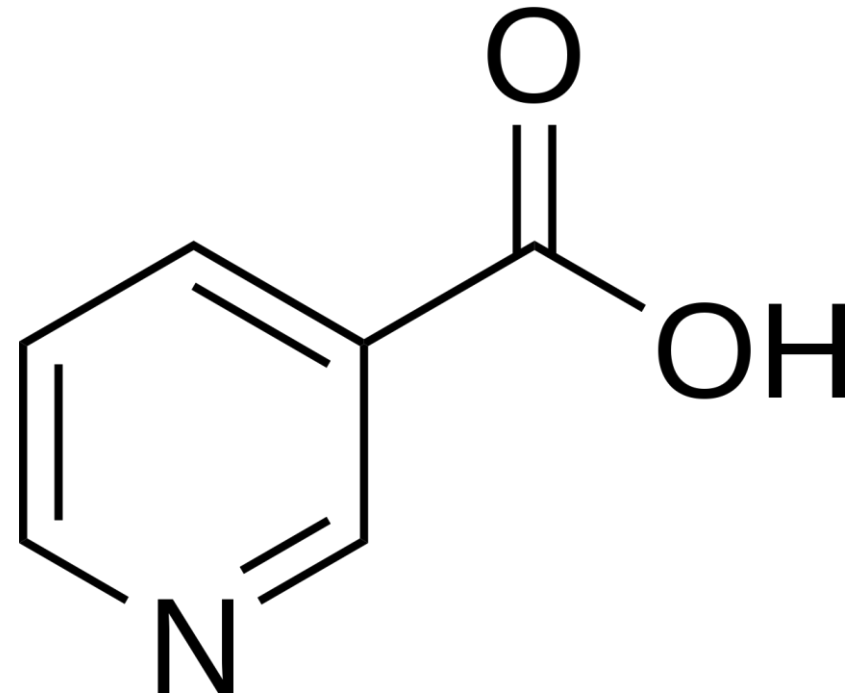
Their findings also reveal genetic connections between 4PY and vascular inflammation, offering opportunities for innovative interventions

A terminal metabolite of niacin promotes vascular inflammation and contributes to cardiovascular disease risk | Nature Medicine

Excessive niacin intake, despite its prevalence in Western diets and fortified foods, can elevate 4PY levels, increasing cardiovascular risk

Dr. Hazen compares niacin intake to filling a bucket; once it overflows, the body produces 4PY

The study explains why niacin has lost favor as a cholesterol-lowering treatment despite its initial promise. Ongoing research is centered on identifying chemical signatures that predict the development of heart disease.



4PY Breakdown

- 1.Niacin Breakdown:** When we consume niacin (vitamin B3), our bodies break it down into different forms.
- 2.Nicotinamide Formation:** One of these forms, called nicotinamide, can change into other substances.
- 3.Production of 4PY:** Nicotinamide can turn into a compound called nicotinamide N-oxide (NNO), which further transforms into a substance called 4PY.
- 4.Impact on Health:** High levels of 4PY may lead to inflammation in blood vessels, which can contribute to heart disease.

Not much is understood about 4PY and what influences it

Oxidative stress:

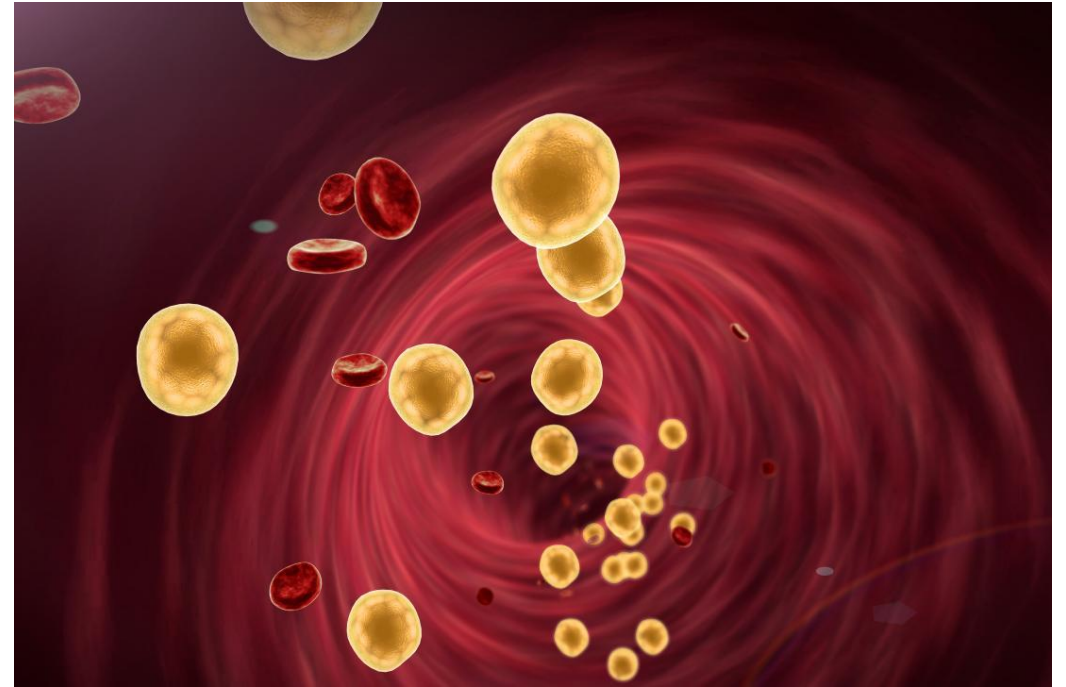
- May modify enzymes responsible for niacin metabolism, potentially disrupting the normal conversion of niacin, leading to 4PY
- Additionally, oxidative stress can cause cellular damage and inflammation, affecting metabolic pathways and potentially increasing the production of 4PY as a byproduct



Dyslipidemia alters lipid metabolism, which includes the processing and utilization of fats in the body

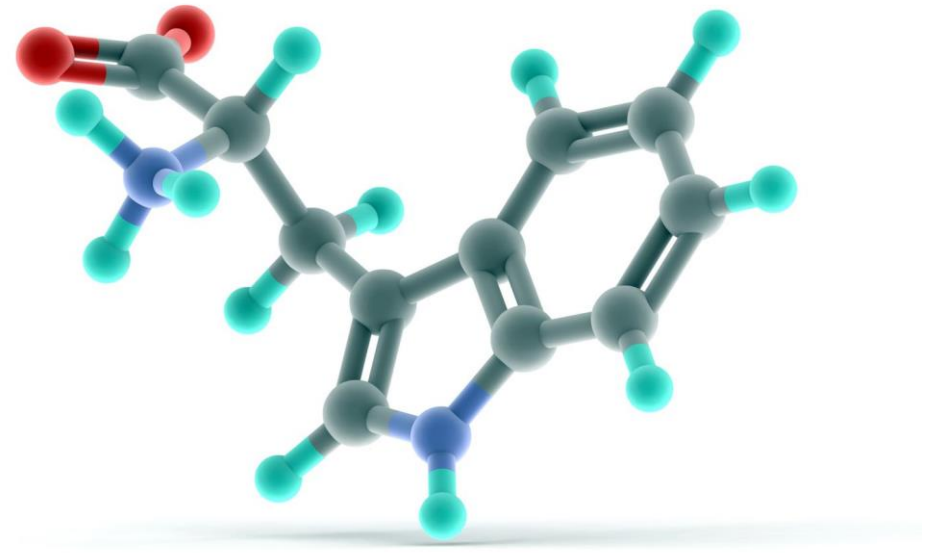
Optimal Lipid Metabolism: When lipid metabolism functions well, fats are efficiently processed and utilized by the body

Niacin Metabolism: Niacin metabolism is closely tied to lipid metabolism, as niacin plays roles in various processes related to fats and cholesterol



Availability of Precursors: In optimal lipid metabolism, there are likely enough lipid-derived precursors or cofactors needed for niacin metabolism (such as tryptophan, B6, iron)

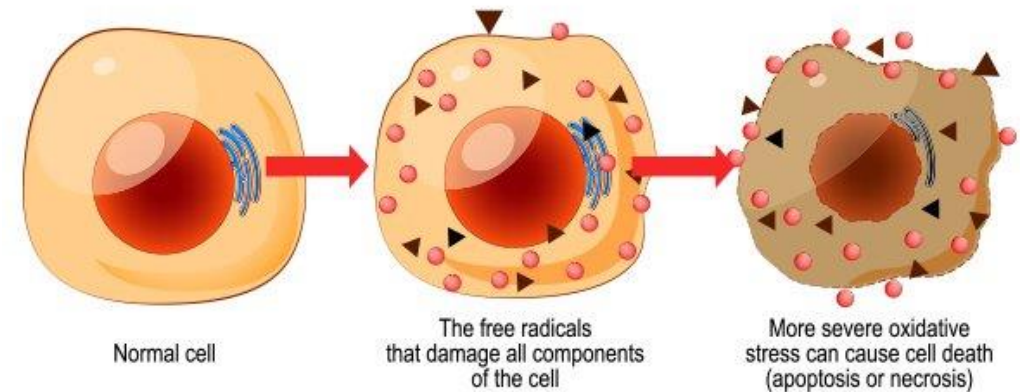
Impact on 4PY Production: With sufficient precursors and cofactors, niacin metabolism can proceed smoothly, potentially reducing the production of 4PY, a metabolite associated with high cardiovascular risk



If participants in studies were not screened for the amount of oxidative stress or dyslipidemia then the niacin may be the victim, not the cause of 4PY

Too much niacin that is not metabolized correctly could explain the excess 4PY and increase cardiovascular risk

Oxidative stress



Synthetic vs Natural Nutrients: Does it Matter? (healthline.com)

Natural nutrients are generally associated with health benefits, but the evidence for synthetic supplements is mixed:

- Some studies suggest a lower risk of heart disease and cancer with multivitamin use
- Others find no effect or even an increased cancer risk

High-dose multivitamin studies show no heart health benefits but potential memory improvements in older adults

However, long-term multivitamin use may not affect brain function or memory in older men

Evidence on single or paired supplements' benefits for heart disease is unclear.

Some studies suggest B vitamins like folic acid may improve brain function, but others disagree

Vitamin D supplements have potential benefits for cancer, bone health, and brain function, but more evidence is needed

Combining vitamin D with calcium can improve bone health in older individuals



Antioxidant supplements like beta-carotene, vitamins A, C, E, and selenium may not reduce the risk of death or cancer and could even increase cancer risk in smokers

Antioxidants might slow the progression of diseases causing blindness, but further research is necessary

In summary, while natural nutrients show promising health benefits, synthetic supplements have mixed evidence, and more research is needed to fully understand their effects



Taking synthetic vitamins can be risky:

The FDA doesn't vet supplement safety, leading to potential inaccuracies in labeling and fraud

Excessive intake of synthetic vitamins, especially fat-soluble ones, can lead to accumulation in the body and hypervitaminosis

Pregnant women should be cautious with synthetic vitamin A to prevent birth defects



Synthetic beta-carotene, vitamin E, and high doses of vitamin A may increase premature death risk

Synthetic multivitamin and iron supplement use may elevate cancer risk

Synthetic folic acid might pose more cancer risk than natural folate

While recommended doses are generally safe, excess synthetic vitamin intake can have harmful effects



Always look to see if studies are using synthetic or natural vitamins

Most likely synthetic – remember they are made in a lab

Accept there is a difference – research supports this

Be wary of observational studies

For double-blind placebo trials – look at what they did not consider

If it is an observation study – it's a correlation, not causation

