



FACT SHEET

Vitamin E meta-analysis in *Annals of Internal Medicine*: What's wrong with this picture?

What is a meta-analysis?

A meta-analysis is not a clinical trial. It is a statistical technique for combining the results of many existing studies in order to clarify possible effects. When studies are done with a few hundred or even a few thousand people, it is often difficult to determine whether differences between the treatment group and the placebo group are “real” or just accidents due to chance. Combining studies provides more people for analysis and thus increases statistical power. While a meta-analysis is an important scientific tool, it also has limitations.

What is all-cause mortality?

Studies are generally designed to look at some particular outcome, like whether vitamin E reduced the risk of having a heart attack. However, in studies involving sick people and lasting for several years, there will be other outcomes, such as death. A certain number of people in longterm studies are going to die, and all-cause mortality is the number of people who died from any cause—whether or not the cause has anything to do with the purpose of the study. All-cause mortality includes people who died of heart disease or infectious disease or cancer or getting hit by a bus. The number of people who die in the treatment group and in the control group will rarely be exactly equal. Statistical analysis tells us whether differences in total mortality between the treatment group and the control group are significant or just the result of chance.

What did this study find, overall?

This study analyzed 19 clinical trials in which vitamin E was given, involving a total of almost 140,000 people. Eighteen of the 19 trials individually found no statistically significant increase in total mortality in the vitamin E group. Even when all of the 19 trials were combined, there was no significant increase in total mortality. The study authors say, “The average death risk across trials in the control groups was 1022 per 10,000 persons. Overall, vitamin E supplementation did not affect all-cause mortality.”

What did the study find, relating to high and low doses of vitamin E?

When the trials were divided according to the dose of vitamin E, the researchers found that low doses of vitamin E slightly decreased total mortality while high doses of vitamin E (400 IU or more) slightly increased total mortality. The researchers said this was a statistically significant effect, but others have criticized whether it has practical meaning. Most of the high-dose studies were done in people who already had various diseases and the authors say that these findings may not be generalizable to healthy adults. However, they go on to generalize, saying that people should avoid high-dose vitamin E and indeed high doses of any vitamin—a conclusion much more sweeping than is justified by their analysis.

Were there other findings?

The researchers also did a dose-response analysis of the clinical trials, which found a statistically significant (but very small) increase in mortality only when the vitamin E dose was greater than 900 IU. This is contrary to the finding in their main meta-analysis that doses over 400 IU might confer increased risk.

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More facts on the vitamin E meta-analysis

What were the 19 studies used in this meta-analysis?

The studies chosen for the meta-analysis all lasted more than one year and reported at least 10 deaths from all causes. Studies in which no deaths occurred were not included in the analysis. The studies were originally published in the decade from 1993 to 2004. Some of the studies involved over 20,000 people, and some involved only a few hundred people. Doses used in the studies ranged from 16.5 IU to 2000 IU and were given for periods from one to 8 years. In some studies the vitamin E was given as part of a multivitamin or some other mixture of nutrients, and in some studies vitamin E was given as a single nutrient. The studies were conducted in various parts of the world—Europe, Asia, the Middle East, Australia, Canada, and the U.S. Vitamin E was given in these studies for many different purposes, including reducing the risk of heart disease, cancer, and macular degeneration and delaying the progression of cataracts, kidney disease, Alzheimer's disease and Parkinson's disease. **Some of the studies found a benefit of vitamin E for these purposes.**

Do any of the studies show a benefit from vitamin E?

Yes. Many of the 19 clinical studies used in this meta-analysis actually showed a health benefit from vitamin E. For example, one study in England showed that vitamin E at levels of 400 and 800 IU reduced the risk of heart attack by 75% in men who already had symptoms of heart disease. A study in patients with kidney failure found a reduced risk of heart attacks and of death from heart disease in people who were given 800 IU of vitamin E. Another of the studies found that vitamin E (400 IU) in combination with some other nutrients reduced the risk of age-related macular degeneration, the leading cause of blindness in elderly people. And one study showed that a very high dose of vitamin E (2000 IU) delayed the progression of Alzheimer's disease.

Do epidemiologic studies show a benefit from vitamin E?

Yes. Numerous epidemiologic studies have shown a benefit from vitamin E. In an epidemiologic study, researchers simply observe whether people who use certain products or adopt certain habits on their own have more or less disease than people who do not. A Harvard study of more than 80,000 nurses found a 41% reduction in the risk of heart disease in nurses who had used vitamin E supplements for at least 2 years. A Harvard study of almost 40,000 male health professionals (mostly dentists) found that men who took vitamin E supplements for more than 2 years had a 37% reduced risk of heart disease. A study conducted by the National Institute of Aging in 11,000 elderly people found that those who used supplements of vitamins C and E had a 53 percent reduction in mortality from heart disease and a 42 percent reduction in all-cause mortality, compared to non-users.

Are more studies being done using high-dose vitamin E?

Yes. A number of new clinical trials are now under way, and researchers are attempting to reassure the people enrolled in these trials that vitamin E is safe and that the research should continue. They include the Women's Health Study involving over 40,000 female health professionals, the Physicians' Health Study involving thousands of U.S. doctors, and the Women's Antioxidant Cardiovascular Disease Study. Also, the National Cancer Institute is sponsoring the Selenium and Vitamin E Chemoprevention Trial (SELECT) to evaluate the effects of these two nutrients in protecting against prostate cancer in more than 30,000 men.

More facts on the vitamin E meta-analysis

Was it reasonable to select 400 IU as the cutoff between low-dose and high-dose vitamin E?

No. Four hundred IU was an arbitrary number. It is not evident how the researchers chose to define 400 IU and not some other value as the “high-dose” mark, except that it is the most commonly marketed dose in the U.S. Two important studies including the GISSI trial in Italy used 330 IU of vitamin E—not much lower than 400 IU. Including those in the high-dose group would have been reasonable, and the positive effects of the GISSI trial would have offset some of the studies showing a trend toward increased mortality. Below that dose, there is only one study at 200 IU, also showing a slightly beneficial effect on total mortality. The truly “low-dose” studies are the five that used only 60 IU or less of vitamin E. In short, it appears that 400 IU rather than 200 or 300 IU may have been arbitrarily selected as the high-dose cutoff in order to bolster a finding of risk.

How much vitamin E is safe?

The Institute of Medicine, a scientific advisory body, has concluded that vitamin E is safe for chronic use in the general population at levels up to 1000 mg (1000 IU synthetic vitamin E, 1500 IU natural vitamin E). The Recommended Dietary Allowance for vitamin E is 15 mg (15-22.5 IU, depending on the chemical form), and only a small fraction of the population gets this much from diet alone. Most multivitamins contain 15 to 60 IU of vitamin E.

What should people think about this meta-analysis?

This meta-analysis does not change what is known about vitamin E safety. It used no new research but instead combined 19 studies in order to create statistical significance for a finding of a slight increase in all-cause mortality in studies that used 400 IU or more of vitamin E, but overall the studies showed no such increase and a dose-response analysis showed a significant increase only at levels above 900 IU. The authors have exaggerated the practical significance of their findings to attract attention and scare the public. As a result, numerous participants in ongoing clinical trials on high-dose vitamin E sponsored by the National Cancer Institute have been needlessly frightened, and the future of the studies may be endangered. **Consumers who are already using vitamin E should continue to use it with confidence, and people who are not currently using at least a multivitamin containing vitamin E should consider doing so, since the overwhelming majority of the population fails to get the recommended amount of vitamin E from diet alone.**