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REPORT

The Making of Killer E

The truth behind the recent vitamin E controversy

By Terri Mitchell

Like an asteroid slamming into the Earth, like a spaceship landing on the White House lawn, last November the news hit that vitamin E increases mortality. Yes, according to researchers at Johns Hopkins, vitamin E is a killer.¹ The vitamin supplement that millions of Americans believe to be a good thing is actually a snake in the grass, waiting to do them in. The findings are so dire, according to the report, that the public should not take any high-dose supplement because, according to the Hopkins researchers, not only are they dangerous, but there is no evidence that they do anything at all.

These researchers were so concerned about the public's health that they advised public health authorities to launch campaigns warning people about supplements. Never mind that the evidence on which these claims are based is a numbers game. Never mind that the evidence is a handful of selected studies mostly involving seriously ill, aged people. Never mind that studies showing that vitamin E might actually prolong life were omitted. And who published this analysis directing every public health official in America to act immediately for the public good? The *Annals of Internal Medicine*—the journal of America's internists. And why did the *Annals of Internal Medicine* publish this alarming report that made headlines all over the world?

Although the authors of the report referred to it as a “study” in their media appearances, it is actually an analysis of existing studies, or a “meta-analysis.” No patients were recruited; not a capsule was swallowed. This meta-analysis is strictly armchair number crunching done by computer, with the input courtesy of others. The motivation behind this meta-analysis was strictly personal interest, according to the lead researcher, Edgar R. Miller III.

THE CHOSEN FEW

Nineteen studies were chosen for the Hopkins meta-analysis.¹ Only studies that lasted at least one year, and in which 10 or more deaths occurred, were considered. Most of the studies used data from people who had one or more chronic diseases—such as serious heart disease, diabetes, Parkinson's, Alzheimer's, and kidney failure—or who were at risk of developing heart disease. For example, one such study, the so-called WAVE study, enrolled only women with at least one artery blocked 15-75%.² Huge studies such as the EPESE study, in which vitamin E's effects on mortality were tracked for nine years in more than 11,000 people, did not make the cuts—perhaps because those taking vitamin E lived longer than those who did not supplement.

Of the 19 studies analyzed, only nine pertain to vitamin E alone.¹ The rest involved combinations of vitamin E and other nutrients.¹ According to the authors, this is valid because they “controlled” for whatever impact these other factors might have had on mortality. When asked how they could control for how other vitamins and minerals affect vitamin E's influence on mortality—given that the impacts are mostly unknown—they responded:

“In this analysis, data from factorial trials were restricted to participants not exposed to the second factorial intervention. In addition, we included other study-specific explanatory variables as second level covariates in the categorical and dose-response hierarchical models. Due to the limited number of trials, we separately evaluated the impact of adding the following variables: gender distribution, mean age, use of other vitamins/minerals combined with vitamin E, and average time of follow-up. Finally, we evaluated the influence of each trial on the results by removing each individual study from the analysis.¹”

The authors of the vitamin E meta-analysis reveal conflicted opinions about vitamin E's effects. As the authors analyzed data, vitamin E's effects mutated from “vitamin E supplementation did not affect all-cause mortality” (their own words) to “for dosages less than 150 IU/d, all-cause mortality slightly but nonsignificantly decreased,” to “Policymaking bodies, which currently do not recommend antioxidant vitamin supplement use to the general



population, should also caution the public against the use of high-dosage vitamin E supplementation.”¹ This is quite a hop, skip, and jump for one publication, so we decided to take a closer look.

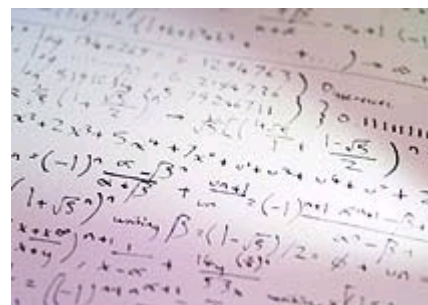
WHAT THE STUDIES ACTUALLY SAY

As noted earlier, only nine of the 19 studies included in the meta-analysis provide data on vitamin E alone—the rest are studies of combinations of antioxidants and minerals. Of the nine studies that provide data on vitamin E alone, seven show no effect on overall mortality (ATBC,⁴ DATATOP,⁵ ADCS,⁶ VECAT,⁷ HOPE,⁸ PPP,⁹ GISSI,¹⁰) one shows a beneficial effect,¹¹ and one, the CHAOS study, shows both a negative effect and positive effect.¹² It is not clear why the CHAOS study was included in the meta-analysis, considering that it has been criticized for faulty methodology. In this study, the vitamin E group had significantly higher serum cholesterol levels and a significantly greater percentage of participants had high blood pressure, diabetes, and severe coronary artery disease. The CHAOS study showed a 75% decrease in nonfatal heart attacks in the vitamin E group, yet an increase in mortality that was not statistically significant.¹² From these studies, which overwhelmingly conclude that vitamin E either did not affect, or was beneficial for overall mortality, vitamin E’s reputation as “killer E” was created. So where’s the killer?

ARMCHAIR SCIENTIFIC RESEARCH

The “killer E” meta-analysis includes only one type of study. Whether called a “prevention,” “intervention,” or “clinical” trial, these studies supply their subjects with up to a year’s worth of vitamins and instruct them to show up in three or four months for evaluation. One way to determine whether the participants are taking the supplements is to have them bring their supply to a visit and count the leftover capsules.

Obviously, this kind of compliance check has its drawbacks. One study states that compliance was measured by “refilling drug supplies every 3 months”; nothing else was done to determine whether the subjects were actually taking their pills.¹⁰ In at least one trial, if the participants did not show up for evaluation, they could still receive their vitamins by mail.¹³ To illustrate how poorly controlled many of these trials were, it was later discovered in the CHAOS trial that 78% of those who died while supposedly taking alpha tocopherol were not in fact taking it.¹² The study’s numbers went from giving the impression that vitamin E kills people to suggesting that vitamin E cuts the risk of heart attack in half—all with the stroke of a pen. According to the researchers, the findings may have “underestimated the true benefit of alpha tocopherol.” By the study’s end, only about 40% of the subjects were still taking their vitamins.¹² Rudolph A. Riemersma, a co-author of the “killer E” meta-analysis, had previously written that the CHAOS trial “was probably too small to examine mortality.”¹⁴ He apparently changed his mind, as the CHAOS study was included in the “killer E” meta-analysis.



HIGHLIGHTS FROM DECADES OF RESEARCH

Results of a four-year study on natural vitamin E and atherosclerosis in monkeys were published in 1992.¹⁶ Atherosclerosis was induced by adding cholesterol to the animals’ diets, and their arteries were examined by ultrasound eight times over the course of the study. At the study’s conclusion, 87% blockage of the common carotid artery was measured in animals eating cholesterol plus placebo. In animals that received vitamin E with their cholesterol, arteries were blocked 18%. Twenty-four areas of the animals’ arteries were examined under a microscope and photographed. The researchers concluded: “At nearly all sites, the values for stenosis and severity rating were lower in the treated animals compared to controls, indicating that vitamin E may be effective in reducing the histopathological effects of an atherogenic diet.”¹⁶ Note something important here: the monkeys’ diet was essentially vegetarian, aside from dietary casein (dairy) protein and experimentally added cholesterol. Vegetarians receive only about 5% of their energy from saturated fat (versus 10% for meat eaters),¹⁷ have greater blood levels of antioxidants,¹⁸ and have far less free radical-promoting iron in their blood.¹⁹ All of these factors may contribute to heart health.



A similar study in humans showed the same effect but to a lesser extent, possibly due to its relatively short duration (six years), dietary factors, and the fact that some of the participants smoked.²⁰ In this study, 500 mg of slow-release ascorbic acid and 272 IU of alpha tocopherol retarded artery blockage, especially in men.²⁰

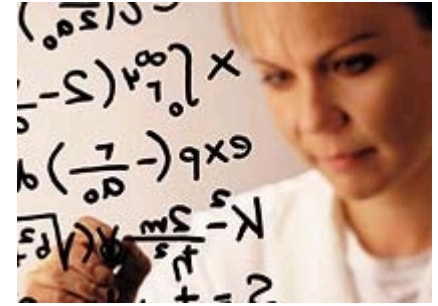
Vitamin E studies are frequently conducted using subjects who already have heart disease. A recent study from Case Western Reserve University demonstrates that vitamin E may also help prevent damage to arteries from angioplasty and from the toxicity of low-density lipoprotein (LDL).²¹ Oxidized LDL prevents endothelial cells from migrating to and repairing damaged areas. Scientists have discovered that alpha tocopherol maintains healing action and overrides LDL’s negative effects. Because other antioxidants (BHT and probucol) did not have the same effect in this study, researchers believe that vitamin E’s effects are the result not of its antioxidant properties, but of its ability to inhibit changes in cell membrane integrity caused by oxidized LDL. They reported that

vitamin E may have properties in addition to its antioxidant action that “could be important in the primary prevention of atherosclerosis and its complications.”²¹

The importance of vitamin E’s antioxidant effects on heart health may be illustrated by a European study that sought to determine why Lithuanian men have a heart disease mortality rate that is four times that of men in Sweden.²² It found that while Lithuanian men actually had lower LDL levels than their Swedish counterparts, their plasma gamma tocopherol levels were about half those of the Swedish men. The researchers concluded, “The high mortality from coronary heart disease in Lithuania is not caused by traditional risk factors alone. Mechanisms related to antioxidant state may be important.”²²

In a University of North Carolina study based on a questionnaire, vitamin E supplements significantly reduced the risk of mortality from breast cancer in women who had been previously treated for it.²³ The women, who were studied for 12-14 years, had to take vitamin E for at least three years to see benefit, which included a significantly reduced risk of breast cancer recurrence.²³

Question: if you are 100 years old and all your friends who were born around the same time as you are now dead, what do you have that they did not? According to one study, the answer is vitamin E. This study tested 50 biochemical markers in the blood and urine in relation to all-cause mortality of people aged 90 to 100. These biochemical, hematological, and biological parameters were measured in six- to 12-month intervals. Serum vitamin E was the only vitamin that was significantly higher in the people who survived.²⁴



A British study found that in people 75 to 84 years old, those with the highest blood levels of vitamin C had about half the risk of dying as those with the least vitamin C.²⁵

The American Cancer Society queried 991,522 US adults about their use of vitamin supplements. Following up 16 years later, it was found that people who took vitamin E supplements for 10 years or longer reduced their risk of death from bladder cancer by 40%.²⁶ Vitamin E supplementation of shorter duration was not protective.

A study conducted by the Centers for Disease Control and Prevention collected information on more than a million Americans. The study results showed that using multi-vitamins along with vitamins A, C, and E reduced the risk of mortality from any cause by about 15% over the course of seven years.²⁷

These and other studies strongly suggest an association between antioxidant status and decreased mortality in older adults.

OVERLOOKED POSITIVE DATA

The following published excerpt is indicative of the controversy surrounding the big intervention studies behind the vitamin E headlines. It addresses the GISSI study, which was included in the vitamin E meta-analysis.

“The investigators’ conclusion that alpha tocopherol is without benefit is inappropriate and misleading. A careful analysis of their findings reveals that alpha tocopherol supplementation resulted in the following significant effects when the more appropriate four-way analysis was undertaken: 20% reduction in cardiovascular death, 23% reduction in cardiac death, 25% reduction in coronary death, 35% reduction in sudden death despite the primary endpoint not being statistically significant.”¹⁵

As evidenced by the percentage reductions above, even investigators conducting large intervention studies can make erroneous conclusions based on the data that they themselves gather. Studies that are a little longer on data and shorter on number manipulation might give a better picture of vitamin E’s effects. That is not to say that large intervention trials are worthless, because they are not. It is questionable, however, whether sweeping conclusions should be drawn and public policy decisions should be made based solely on a handful of carefully selected, highly controversial intervention trials.

Studies that examine how much vitamin E is in a person’s blood, or that evaluate vitamin E’s effects on the heart and arteries under controlled conditions, may give a more accurate picture of what vitamin E can do.

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BEHIND THE HEADLINES, CONTROVERSY RAGES

The ink was barely dry on the “killer E” meta-analysis before the criticism erupted. Experts of all kinds, including doctors, dieticians, and medical researchers, have questioned the validity of the analysis: “one might well expect that they should produce conclusions that are consistent with the authors’. This, unfortunately, is not the case . . .”; “You describe the pooled risk difference . . . But when I add the numbers . . . I get a risk difference of . . .”; “. . . this *Lancet* study made an entirely different conclusion from your above study . . .”.²⁸ The controversy will rage for months, if not years. Its effect will be positive, as more attention will be paid to the design of future antioxidant clinical trials, and the inadequacies of such studies in general will become more widely recognized.

But the question remains: why did the *Annals of Internal Medicine* publish such nonsense? The answer was clearly stated in that same publication. The point was to make public policy. The “killer E” meta-analysis was a call for an end to all “high-dose” supplements, a dare to American institutions to reverse their policies on vitamin E, and a challenge to “regulators and policymakers” to control which vitamins Americans take. Who are these people who want to control which vitamins we take?

The study authors are not unfamiliar with the glow of headlines. In the *New England Journal of Medicine*, they claimed that fish oil increases heart attack risk,²⁹ a claim that was refuted in the same issue by a different research group.³⁰ The editor who published the “killer E” meta-analysis in the *Annals of Internal Medicine* has a long history of trying to dictate public policy, and has announced that he is using that journal as the mouthpiece for a committee that he formerly chaired, known as the US Preventive Services Task Force.³¹ Among other things, he acknowledges only meta-analyses and mega-clinical trials as bona fide scientific evidence, and has led the “task force” in assigning “ratings” to the value of such things as prostate cancer screening (no approval), vitamin use (no approval), and cost-benefit analyses (strong approval).³¹⁻³³

In upcoming issues, Life Extension will be telling members more about what this editor, his “task force,” and others have in store for you. Stay tuned for more sequels to the “killer E” meta-analysis, coming to a newspaper or website near you in the new age of “shared decision making” and sensational “science.”



SYNTHETIC VS. NATURAL VITAMIN E

Because it is less expensive than natural vitamin E, synthetic vitamin E is often used in research studies. Many of the studies that make up the Hopkins vitamin E meta-analysis used synthetic vitamin E instead of natural d-alpha tocopherol.¹ The researchers tried to account for this difference by converting all vitamin E dosages in the studies to international units based on the relative biological activity of synthetic vitamin E. Natural and synthetic vitamin E, however, are biochemically distinct, and thus this method of comparing them may not be highly accurate.

Alpha tocopherol is the most biologically active form of vitamin E,³⁴ and its natural form consists of one isomer. By contrast, synthetic vitamin E is a mixture of eight isomers, of which only one occurs in nature and is thus compatible with human body chemistry. Very little research has been done on the separate pharmacology of the other seven synthetic, unnatural isomers. The pharmacology of synthetic vitamin E is quite different from that of natural vitamin E; it demonstrates an entirely different dose-response curve, proving that it is an entirely different drug by modern pharmacological standards. The two supplements are not equivalent at any dosage ratio.³⁵ Strangely, only in the case of synthetic versus natural vitamin E do scientists ignore the rule that different isomers are different drugs, and that different dose-response curves produce entirely different effects.

The body processes vitamin E by the same enzyme pathway that metabolizes up to 40% of prescription drugs.^{35,36} Because it consists of eight isomers, synthetic vitamin E may have a greater potential of interacting with and modifying the effects of prescription drugs than does the single isomer that makes up natural d-alpha tocopherol.

The vitamin E meta-analysis not only failed to differentiate between natural and synthetic vitamin E, but also did not distinguish between different fractions of vitamin E. Alpha tocopherol is the most predominant form of vitamin E in the human body, and is the form most frequently sold as a supplement. There are three other tocopherol forms of vitamin E: beta, delta, and gamma. Until recently, no one thought there was much difference between alpha tocopherol and other forms of vitamin E. In light of recent research, however, such thinking is on the way out.

In recent years, gamma tocopherol has moved to the forefront of nutritional research. Gamma tocopherol is found in the muscles, veins, skin, and fat, in contrast to alpha tocopherol, which is often found in the blood and cell membranes.³⁷ Taking supplemental alpha tocopherol changes the body's ratio of alpha tocopherol to gamma tocopherol, lowering serum levels of gamma tocopherol.³⁸ Gamma tocopherol has biological actions that alpha tocopherol does not, including anti-inflammatory properties.³⁹ Thus, any ill effects from supplemental alpha tocopherol may be due to its tendency to lower serum levels of beneficial gamma tocopherol. (See also "American Medical Association Discovers Gamma Tocopherol," *Life Extension*, January 2005.)

MISCONCEPTIONS ABOUT VITAMIN E

A staggering 24% of Americans take vitamin E. For most nutrition-conscious people, vitamin E is synonymous with "antioxidant," which is synonymous with anti-aging and anti-heart attack. This sound-bite version sounds good, but is not exactly accurate. While vitamin E has numerous proven benefits, it cannot be expected to reverse advanced heart disease, to single-handedly stop aging, or to cure anything else that comes along. Vitamin E is a victim of its own success, and we may need to reassess our conceptions of it.

Not only is vitamin E not a wonder drug, but its most common form (alpha tocopherol) may not be as powerful as some of its cousins. There are eight known forms of vitamin E—four tocopherols and four tocotrienols—and all can be called "vitamin E." Each is responsible for unique actions in the body, and the benefits of each continue to be discovered.

Vitamin E is a fat-soluble antioxidant, but not all free radicals occur in fat; some occur in watery parts of the body like blood. Different types of free radicals require different types of antioxidants, which is why supplements are sometimes advertised as providing antioxidant protection that is hundreds of times stronger than that provided by vitamin E. The advertisements are accurate: some supplements are hundreds of times more powerful than vitamin E against certain types of free radicals. Vitamin E is by no means the beginning and end of antioxidants, nor is alpha tocopherol the sum total of vitamin E; unfortunately, in many medicine cabinets, a bottle of alpha tocopherol is the beginning and end of antioxidants.

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