Designed to fail: a trial without meaning

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It is unfortunate when researchers waste funds on studies that are unlikely to provide useful results. The recent Harvard study by Howard Sesso and colleagues, the Physicians' Health Study II, evaluating the role of vitamins C and E in heart disease over a 10-year period, published in the *Journal of the American Medical Association* (*JAMA*),[1] falls into this category. A few years ago, Hickey and Roberts described specific ways to design a trial to show the absence of a benefit from these vitamins in heart disease.[2] The new study follows these rules intended to illustrate study bias almost to the letter, forcing us to repeat some basic rules of research into nutrition.

Dr Hilary Roberts, on reading the newly published Sesso *et al* study, said:

"We intended our advice to show how NOT to perform a trial of vitamin C and E in heart disease. Perhaps someone should explain that to them".

Natural vs synthetic vitamin E

One rule was to use the wrong type of vitamin E. Vitamin E is not a single substance, but a range of at least eight substances (tocopherols and tocotrienols).[3] The different forms of "vitamin E" have distinct biological properties.[4,5] The form of vitamin E used in the Sesso *et al*. study was synthetic dl-alpha-tocopherol. This is less effective than the natural forms, and is quite different in biological function and antioxidant activity than the predominant form in the diet[6] (as found particularly in vegetable oils); using synthetic vitamin E thus minimises the possibility of finding benefit. Indeed, its use may interfere with the beneficial effects of natural vitamin E by competitively inhibiting or blocking receptor sites for the natural forms.[7] The study also ignored the impacts of the all-important four tocotrienol isomers[8] found in natural vitamin E.

The other vitamin evaluated in the Physicians' Health Study II was vitamin C. This form was also synthetic and lacked the common synergists normally associated with good quality vitamin C supplements, namely citrus derived bioflavonoids, which have been associated with a reduction of heart disease risk factors such as blood triglycerides.[9]

Dosage

Another rule was to use too low a dose. The vitamin E dose in the study (400 IU every other day) is insufficient to act as an antioxidant in humans. This study has no relevance to people taking natural tocopherols or tocotrienol supplements at appropriate doses. In other words, the study does not apply to people who supplement with vitamin E.

Similarly, Hickey and Roberts predicted that a dose of up to 500mg vitamin C would have minimal or no effect in preventing heart disease. The daily dose of vitamin C used by Sesso *et al*. (500mg) is only half a typical one-gram tablet, of the type popular with supplement users. Dynamic flow levels of vitamin C, which may prevent heart disease, begin at daily intakes above about 3g per day, taken in divided doses (this is a minimum level – higher doses may be needed, depending on individual physiological requirements). A dose of 500mg will only marginally raise median blood plasma levels above the baseline level of 70 microM/L and thus be ineffective. For those in the study with pre-existing heart disease (754 men in a total population of 14641), the appropriate vitamin C intake is higher still.

Placebo problems

Both the vitamin C and vitamin E supplements were compared with a "placebo", but the nature of the placebo was not clarified. This is an important omission in a nutritional study, since the placebo could have contained substances, such as magnesium, which have a beneficial nutritional effect in heart disease.

This raises a fundamental problem of applying randomised controlled trials to the field of nutrition; you cannot apply a true control given that all subjects are exposed to food, if not supplements, and any balanced diet contains substantial amounts of nutrients, many of which interact synergistically. In scientific terms, the occurrence of uncontrolled elements of the diet in both the control and treatment groups introduces confounding that is likely to interfere with any meaningful biological effects, particularly if the dosages are low, as they indeed were in the Physicians' Health Study II. In addition to this, given that the study involves physicians, it is likely that the subjects, with their greater knowledge of health issues, would have consumed diets that are more healthy than those of average Americans.

The study also ignores the typical combinatorial effects of supplement usage, coupled with healthier lifestyles. As Michael Pollan asserted in his book "*In Defense of Food: An Eater's Manifesto*" (Penguin, 2008), be a supplement user, as they do most things better, including eating healthier diets, taking more exercise and generally living healthier lifestyles.

Using statistics as a means to an end

The claim that the "vitamin E" was associated with an increased risk of haemorrhagic stroke could also be irrelevant. The study employed numerous statistical tests of subgroups, with a confidence limit set at one in 20 ($p<0.05$). Repeated testing of subgroups will, by definition, result in apparently significant results due to chance alone (roughly one in every twenty tests). While a confidence limit of one in twenty is appropriate for a single statistical test, it is not suitable for repeated testing of the same data. In this case, the number and nature of the tests was not made clear and the statistical interpretation was inappropriate.

Conclusions

Sesso and colleagues conclude that the results of their trial "provide no support for the use of these supplements in the prevention of cardiovascular disease in middle-aged and older men." A more accurate conclusion might have been: the trial provides no evidence that supplementation of low doses of synthetic vitamin C and E, when taken by over 50-year-old physicians over a relatively short period of 10 years, has the capacity to prevent cardiovascular disease. However, as the study authors themselves concede, the initiation of supplementation may have been too late to significantly affect the aetiology of heart disease.

We have argued also that the low doses, inappropriate synthetic forms and absence of other natural nutrients and synergists in combination, would—quite predictably—not have the ability to prevent heart disease. Sesso *et al*'s trial was therefore a trial doomed to fail!

But, with three drug companies supplying the vitamins for the trial, namely BASF Corporation, Wyeth Pharmaceuticals and DSM Nutritional Products (formerly Roche Vitamins), maybe this was a surer way of protecting the drug companies' core competence, which is clearly in the field of patented pharmaceuticals, rather than in unpatented synthetic vitamin products?

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