Response from Patrick Holford

ANTIOXIDANT REVIEW IS A STITCH UP

Today's review of trials on antioxidants in the Journal of the American Medical Association fails the four key tests of 'publication bias'. **For the following reasons I suspect it's an attempt to demote vitamin therapy so we keep taking the drugs.**

The first way to investigate whether an analysis of studies is biased is to read the summary, and see if it correlates with the actual result. The conclusion of this study says *'treatment with beta carotene, vitamin A, and vitamin E may increase mortality'* creating the impression these antioxidants are no good. What it fails to say, all of which are clearly shown in the results, is that '*vitamin C given singly, or in combination with other antioxidants, and selenium given singly or in combination with other antioxidant supplements may reduce mortality'*. It also fails to say that *'beta-carotene or vitamin A did not show increase in mortality if given in combination with other antioxidants'*, or that *'vitamin E given singly or combined with 4 other antioxidants did not significantly influence mortality'*. **If you can have one take home message it is that antioxidants are team players and reduce mortality in combination, and that vitamin C and selenium are more beneficial than beta-carotene or vitamin A.**

The next way to investigate whether an analysis is a stitch up is to see if all trials are included, how trials are excluded, and what the trials actually say. Two classic primary prevention studies, where vitamin E is given to healthy people, are those of Stampfer et al, published in the *New England Journal of Medicine*, the first of which gave 87,200 nurses were given 67mg of vitamin E daily for more than two years. A 40 per cent drop in fatal and non-fatal heart attacks was reported compared to those not taking vitamin E supplements.[i] In another study, 39,000 male health professionals were given 67mg of vitamin E for the same length of time and achieved a 39 per cent reduction in heart attacks.[ii] Guess what? They are not included.

Bjelakovic's analysis goes on to further degrade antioxidants by deciding which trials (usually the positive ones) are high bias, then excluding them, and which trials are low bias (usually the negative ones) and only adding these together. I don't agree with how this is done. For example, it is well known that taking statin drugs, that lower cholesterol and induce CoQ10 deficiency, make vitamin E harmful by turning it into an oxidant. This is an obvious bias but the authors don't even mention this. Once you exclude these trials vitamin E has an overall positive effect.

The next test is to see if the most negative studies were actually negative. These studies can skew results on an overall analysis. One of the studies most cited to show increase risk of gastrointestinal cancer is that of Correa et al. So I read the actual paper and contacted the author, Dr Pelayo Correa from the pathology department at the Louisiana State University Health Sciences Centre in New Orleans, and asked about the increased risk he had supposedly found. He was amazed, he said, because his research, far from being negative, had shown clear benefit from taking vitamins.

His study, published in the *Journal of the National Cancer Institute*, had involved giving people with gastric cancer either beta-carotene, vitamin C or antibiotics to kill off the stomach bacterium *Helicobacter pylori*. All three interventions produced highly significantly improvements, causing substantial regression of gastric cancer. Correa and his colleagues had concluded: 'dietary supplementation with antioxidant micronutrients may interfere with the precancerous process, mostly by increasing the rate of regression of cancer precursor lesions, and may be an effective strategy to prevent gastric carcinoma'. No evidence of increased mortality there.

In fact, as Correa told us, there was no way the study could show anything about mortality. 'Our study was designed for evaluation of the progress of precancerous lesions,' he said. 'It did not intend, and did not have the power, to study mortality and has no value to examine mortality of cancer.'[iii] Without this study the main conclusion, that antioxidants may increase gastrointestinal cancer, becomes completely invalid.

So, I'm afraid this 'meta-analysis' fails all four tests of publication bias. The summary at the front refers to negative results only, not the positive results. Some key positive studies have not been included. Positive studies have become negative studies by jiggling the statistics. Known dynamics that would bias some studies towards a negative effect have been ignored. In conclusion, I will keep doing what I've always been doing, because this study confirms it - and that is to supplement a combination of antioxidants, including selenium and high dose vitamin C, because, as this study says, it seems to make you live longer and reduce your risk of premature death.

Patrick Holford is co-author of Food is Better Medicine Than Drugs. See www.foodismedicine.co.uk for his in-depth feature on the 'antioxidant myth'.