In 1989 in an article entitled ‘Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity’ that appeared in the New England Journal of Medicine Daniel Steinberg et al. highlighted the potentially important role of oxidation of low-density lipoprotein (LDL)-cholesterol in atherogenesis. This laboratory work led epidemiologists to examine the association between intake of antioxidants (substances that might stop the oxidation of LDL-cholesterol such as beta-carotene) in the diet of free-living humans and subsequent cardiovascular disease.

Observational studies reported a significantly lower risk of cardiovascular death in those who ate diets rich in beta-carotene. In a meta-analysis the pooled relative risk reduction was 31% (95% CI: 41–20%, P < 0.0001) when those with high beta-carotene intake or serum beta-carotene levels were compared with those with low intakes or levels.2 Several trials of beta-carotene, which had been set up to examine the effect of antioxidants on cancer incidence then reported their results in the mid 1990s. The randomized trials did not confirm the beneficial association seen in observational studies. Instead, they reported a moderate adverse effect of beta-carotene supplementation with a relative increase in the risk of cardiovascular death of 12% (95% CI: 4–22%, P = 0.005).2 The results of these six observational studies and four randomized trials are summarized in Figure 1.

Various explanations have been put forward to explain the results of the beta-carotene trials. These include the suggestion that the trials had not used the correct isomer,3 that the wrong dose was used, that beta-carotene was used alone rather than with other components of fruits and vegetables (a major dietary source of beta-carotene)4 and that the duration of the trials was too short.5 The detrimental effect observed in the beta-carotene trials perhaps seems less surprising when you realise that in the Alpha-Tocopherol Beta Carotene Cancer Prevention Study, for example, 34% of those allocated to receive beta-carotene...
reported skin yellowing at some point compared to 7% in the control group.6

The apparent protective associations seen in the observational studies between high dietary beta-carotene intake and cardiovascular disease was probably due to confounding. People who consume a diet rich in beta-carotene will eat more of the dietary constituents closely associated with beta-carotene. They are also less likely to be smokers and less likely to belong to the socially and economically disadvantaged strata of society.7

Two observational studies published in this issue of the journal attempt to look beyond beta-carotene. The paper by De Waart et al. examines the association between serum measures of six different carotenoids (including beta-carotene), alphatocopherol, various composite indices and all-cause mortality. The strongest protective associations observed with individual carotenoids were with lutein and beta-cryptoxanthin. For lutein the multivariate relative reduction in the risk of death was 36% (95% CI : 5–57%) between lowest and highest tertiles of serum levels. For beta-cryptoxanthin the multivariate relative reduction in the risk of death was 34% (95% CI : 0–57%) between lowest and highest tertiles of serum levels. The size of these protective effects is similar to that seen for beta-carotene and cardiovascular disease reported in previous studies. The study was small, comprising 638 men and women aged 65–85 who were followed up for just over 7 years during which period 171 people had died. Also no carotenoids were a priori believed to be any more protective than any others. Furthermore, the authors do not discuss the determinants of the plasma levels of these different carotenoids nor do they justify the combination of carotenoids into various antioxidant indices.

The paper by Lui et al. examines the association between vegetable intake and coronary heart disease in 22,071 US male physicians followed up for 12 years during which 1148 incident cases of coronary heart disease occurred. After adjustment for a number of confounders the relative risk reduction for each serving of vegetables was 17% (95% CI : 2–29%). The effect was more marked in certain subgroups (those with a body mass index over 25 and current smokers) but as these subgroup analyses were not pre-specified these results should be interpreted with caution. The overall finding is consistent with the results of other observational studies that suggest that increased fruit and vegetable intake is associated with lower risk of coronary heart disease and stroke8,9 but a number of areas of uncertainty about the nature of the association between fruit and vegetables and cardiovascular disease remain.10 The food frequency questionnaire used provides a relatively crude measure of fruit and vegetable intake and though the authors report that they did look at different types of fruit and vegetables their ability to identify more or less protective food groups was probably limited.

Both of these papers support the notion that diets rich in fruit and vegetables are at worst non-toxic and at best are cardioprotective. Neither study, however, takes us a long way further in defining more closely which (if any) fruits and vegetables are cardioprotective and which (if any) constituents of fruit and vegetables are cardioprotective. The only way to prove that individual carotenoids reduce morbidity and mortality from cardiovascular disease will be through further randomized controlled trials. But are we really going to carry out randomized trials on all the potentially bioactive constituents of fruit and vegetables alone and in combination when we don’t even know if the observed protective association with fruit and vegetables is real? In the face of such uncertainty surely a more logical approach is to carry out food-based trials randomizing people to advice to eat more (and/or provision of) fruit and vegetables or placebo. Such trials (if they managed to achieve sufficient prolonged dietary differences) would establish whether increasing fruit and vegetable intake is indeed beneficial to health.

References
5 Steinberg D. Clinical trials of antioxidants in atherosclerosis: are we doing the right thing? Lancet 1995;346:36–38.