Chapter 4. Limitations

Literature

Our search procedures for randomized controlled trials were extensive and included canvassing experts regarding studies we may have missed. In addition, we observed little to no evidence of publication bias via visual inspection or formal testing for the vitamin E studies. However, we acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search and the lack of statistical evidence of the existence of bias. Publication bias may occur for a variety of reasons, including investigators' loss of interest in the study if "negative" results are found or if results are obtained that are contrary to the interest of the sponsor or investigator.

Quality of Trials

An important limitation common to many systematic reviews, whether or not a formal meta-analysis is conducted, is the quality of the original studies. Only a third of our trials scored a three or greater using the Jadad method to assess quality. It has been suggested in the literature that there is a possibility of bias in trials that score lower than this. Other elements of the design and execution of studies have been proposed as measures of quality. For example, the Linxian trial was not designed to assess CVD outcomes as its primary purpose, hence the baseline data on CVD was not as complete as some of the other studies. However, recent attempts to define elements of study design and execution that are related to bias have shown that in many cases, such efforts are not reproducible and do not distinguish studies based on their results.

Appropriateness of the Intervention and Population

A proposed explanation for the lack of effect reported in many of the reviewed studies is that the antioxidant was not administered in a sufficient dose or combined with other agents essential for its success, or given for a long enough period of time, or not given to a population sufficiently likely to benefit. One of the explanations given for the GISSI fatal myocardial infarction results is that the vitamin E may have been better absorbed due to the higher fat content of Italian breakfasts. Many of the vitamin C trials have been criticized as administering too low a dose of vitamin C. Both the GISSI study and the HOPE study were stopped early due to evidence of benefit of other intervention arms. It has been suggested that if these studies were allowed to continue longer a benefit of antioxidants would have become more apparent. Some experts have called for new ways to identify populations most likely to benefit, such as selection participants based on some measure of oxidative stress or low levels of antioxidants. The results reported here cannot necessarily be extrapolated to populations and interventions other than those included in the original studies. Whether higher doses or different formulations of antioxidants or using them for a longer duration will prove more effective is unknown. The findings we report here make it less likely, in our view, that a particular population and antioxidant intervention will be found that proves to be markedly beneficial.

Heterogeneity

Heterogeneity existed in the trial design, populations, size, interventions, and outcomes. This affected our ability to pool studies. We made clinical judgments about pooling studies and describe these explicitly. Many reviewers suggested different combinations of studies to pool, or to avoid pooling altogether. We tested other combinations of studies in sensitivity analyses; no difference in results were seen. Furthermore, almost without exception individual studies also failed to demonstrate a benefit of antioxidant supplementation. Therefore, while there was heterogeneity among studies, we do not think our choices for pooling studies introduced significant bias in either direction.

In addition, a large number of trials reported on the effects of vitamin E in various combinations. To the extent that other agents in the formulas had stronger or contradictory effects to the antioxidant of interest, a potential confounder that we cannot control could have been introduced into the analysis, given the available data.