Carl Atkins suggests that the increase in the partitioned post-treatment hazard ratio for disease-free survival does, indeed, represent a “material loss”. To clarify, no material loss was seen with switching to exemestane compared with the (known) continued effect of tamoxifen—i.e., the upper 95% CI is not much above 1.00. We have referred to the possibility of a carry-over effect for the switch strategy in the article’s discussion. We also disagree with Atkins that the result for improved overall survival in the oestrogen-receptor positive/unknown subset is paradoxical because CIs for the 2.5 year point included 1.0; we note that this is a single time-specific estimate and argue its result is not inconsistent with showing that survival is better in the exemestane group. It is clear from figure 5 that the survival curves do not cross back and forth, rather the curves begin to diverge after 2 years. The log-rank test used to compare all differences in the survival curves does indeed have a null hypothesis that the survival curves are the same. However, our results led us to reject the two-sided null hypothesis, thus providing evidence of a benefit in terms of overall survival for the switch to exemestane compared with continued tamoxifen. This is reiterated in the hazard ratio estimate from the Cox proportional hazards model being less than one (i.e., favouring exemestane).

In response to Masatsugu Ueda and colleagues, although the switch strategy is achieved at the expense of some detriment to skeletal health, the absolute skeletal loss over the 5-year endocrine treatment period is minimal. Later this year we should be able to provide 5-year data from the Intergroup Exemestane Study (IES) on implications of switching strategies on the long-term quality of life. Ueda and colleagues suggest reanalysis of survival, including patients who relapsed before switching. Patients from IES eligible for randomisation into the study were those who remained disease-free after 2-3 years initial tamoxifen therapy. We do not have information on the larger population from which those patients were derived; thus, the proposed analysis is not possible.

We declare that we have no conflict of interest other than those stated in the original paper.

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Folate and ageing

The FACIT trial of folate acid supplementation in older adults by Jane Durga and colleagues (Jan 20, p 208)1 adds to the growing evidence of the importance of folate to the nervous system at all ages, including ageing, cognitive function, and some dementia.2

It is exactly 40 years since I reported in The Lancet the beneficial effects of folate acid on cognitive function and mood in an open study of 26 folate-deficient patients with epilepsy.3 The positive outcome in this and the FACIT trial might reflect the fact that in each the patients were treated for up to 3 years. The transport of the vitamin in the form of methyl folate into the nervous system is strictly limited by an efficient blood–brain barrier mechanism, and clinical responses are invariably very slow.4 In a double-blind, placebo-controlled trial of methyl folate plus standard psychotropic medication for 6 months in 41 folate-deficient patients with depression and schizophrenia, the significant clinical and social recovery due to the vitamin increased over time.4

Durga and colleagues selected patients with raised plasma homocysteine and normal serum vitamin B12 for study. Although the baseline folate concentrations were the same in the two groups, whether any of their patients were folate deficient, and if so whether this influenced the outcome is unclear. However, evidence suggests that folate acid can influence nervous system function at all ages, whether or not a deficiency state exists.5,6 I declare that I have no conflict of interest.

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Authors’ reply

Edward Reynolds’ pioneering work on one-carbon metabolism and psychiatric disease served as an impetus for our own trial.

Our sample size and distribution of folate concentrations did not allow for a thorough investigation of possible effect modification by folate status. A priori, we decided to test whether initial folate concentrations modified the 3-year folate acid effect on cognitive performance by using an arbitrary cut-off point: the population median at baseline (659 nmol/L). We found no significant interaction between initial folate status and the effect of folate acid on cognitive performance.

Nevertheless, our data suggest that those with the lowest concentrations of folate benefited the most from folic acid.
In the FACIT trial,\(^1\) Jane Durga and colleagues found that folic acid supplementation improved cognitive function in elderly people. Although some lipids were measured before and after the intervention, docosahexaenoic acid (DHA, 22:6 n-3) was not. DHA is an essential omega-3 fatty acid which is a critical component of neural membranes. Increased blood concentrations of DHA protect against cognitive decline, an effect that is thought to be mediated by increased neuroprotectin D1 and reduced amyloid production.\(^2,3\)

The major form of circulating DHA phospholipid is phosphatidylcholine, which is released by the liver through a methylation process requiring folate derivatives.\(^4\) Plasma DHA concentrations are associated with the folate concentration in human red blood cells and, in animals, supplemental folate has been shown to increase the circulating DHA concentration.\(^5,6\)

Some of the reduced cognitive decline produced by folate supplementation in the FACIT trial could be mediated by DHA. Future studies could assess this possibility by measuring DHA concentrations before and after dietary folate supplementation.

I have no financial or contractual agreements that cause a conflict of interest.

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**Complementary therapies in juvenile idiopathic arthritis**

We welcome the Seminar on juvenile idiopathic arthritis by Angelo Ravelli and Alberto Martini (March 3, p 767),\(^1\) particularly the sections on epidemiology and clinical features.

Many patients with juvenile idiopathic arthritis use complementary therapies.\(^2\) These range from those with little scientific rationale, such as copper bracelets, to those that might have some scientific merit, such as omega-3 fatty acids, glucosamine, calcium, and vitamin D. Some patients also use folk remedies, such as spraying or rubbing “penetrating” oils on joints to cool them (WD-40, kerosene, and lighter fluid are popular in rural North Carolina)\(^3\) or drinking herbal teas or vinegar. Some patients alter their diets to exclude foods such as those in the nightshade family, gluten, or dairy products. Many patients turn to faith and prayer. Perhaps most commonly, patients rub (massage) the affected joints.

A review of the prevalence, effectiveness, cost, and safety of these approaches would be a useful contribution to clinical practice.

We declare that we have no conflict of interest.

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