Clarke’s cognitive ageing with B vitamins meta-analysis ridiculed

Last year we reported on an erroneous meta-analysis apparently showing that B vitamins do nothing to slow age-related cognitive decline. The research paper is question, authored by Robert Clarke, was so full of holes it was close to being fraudulent, and certainly a gross misuse of science, either out of ignorance or intent.

The American Journal of Clinical Nutrition has, this month, published reviews of the study by two leading expert groups on dementia. The first, heading by Peter Garrard from the Neuroscience Research Centre, University of London, starts by saying ‘Although the sheer volume of data incorporated into this analysis testifies to the industriousness of its authors, few other conclusions can be drawn.’ Clarke’s meta-analysis was a study of studies, excluding anyone who actually had memory problems, with the apparent intention of measuring whether B vitamins would enhance memory or slow decline. Garrard points out “the first [mistake] arises from the enforced adoption of composite measures such as the Mini-Mental State Examination (MMSE) as indexes of cognitive aging. Although undoubtedly useful as markers of dementia severity, these summary measures are not only notoriously insensitive to mild cognitive change but also remarkably stable over time in populations of healthy elderly individuals, meaning that as indexes of cognitive aging they have little practical use.” They then pull to pieces the studies involved in the context of not being suitable or designed to measure changes in cognition in healthy adults. They conclude by saying “Finally, we would question the lead author’s highly tendentious statement that the findings of this study of cognitive aging show that “taking folic acid and vitamin B-12 is sadly not going to prevent Alzheimer’s disease.” There is first-rate scientific evidence that homocysteine lowering with the use of B vitamins confers both biological and neuropsychological benefits on individuals with the clinical syndrome of mild cognitive impairment. We are deeply concerned with the impact that unjustified claims may have on individual members of the public and on policymaking and research funding organizations who, in the absence of opportunities to examine the details of the constituent studies, may allow themselves to fall under the tyranny of very large numbers.” He is right to raise this concern. We know of important trials that have had their funding pulled because of the belief created by this terrible meta-analysis hell bent on saying that B vitamins do nothing.

The second review by an expert group, headed by Emeritus Professor David Smith from Oxford University, points out three major flaws –

- the choice of trials
- the cognitive assessment tools eg MMSE, and
- the analysis and interpretation of data.

On the choice of trials they say “Among the 11 trials in 22,000 individuals included in the meta-analysis, 3 trials had only final test scores and so cognitive change could not be assessed. For the remaining trials, the placebo group did not show significant cognitive decline, the significance of any apparent decline was not reported, or the original article did not report cognitive test results at all. The shortcomings in trial design and flaws in the original reports suggest that these trials should have been excluded from the meta-analysis.” So, if the placebo group has no measurable change in cognition from beginning to end the only way you’d see anything different with B vitamins would be if they actually improved memory in a highly insensitive test. The critical issue is not whether B vitamins make a normal memory super-normal but whether B vitamins prevent cognitive decline. For that you have to have placebo groups getting worse.
They too point out that “The MMSE is a screening test for dementia and is not sensitive for cognitive aging. Because of these limitations of the MMSE, the individual trials using this test were doomed to fail.”

The expert group’s third concern is “the analyses and interpretation of the results. For instance, the authors did not identify subgroups and risk groups in each individual trial that were likely to benefit from B vitamins.” They did not, for example, look at the effects of B vitamins in those with raised homocysteine levels such as the FACIT trial. Professor Smith and colleagues write “Thus, in FACIT [trial], subjects were recruited on the basis of elevated homocysteine (>13 mmol/l), i.e., a subgroup likely to benefit. Indeed, the subjects who received folic acid for 3 y showed benefits in several cognitive domains. So, we find it surprising that the authors of this meta-analysis consider the results of FACIT trial as due to “chance,” given that this study had a better design for testing cognitive change than most of the other trials.”

Robert Clarke, the author of the discredited meta-analysis, had an opportunity to reply to these criticisms but failed to address them in any meaningful way. For example, he justified his use of the MMSE test by citing two research studies on dementia using the MMSE but seemed to forget that none of the trials in his meta-analysis were on dementia patients – they were excluded.