

## Supplementation and the Elderly: Dramatic Results?

*To the Editor:* We read with interest Chandra's randomized, double-blind, placebo-controlled trial of a supplement of trace elements and vitamins on cognitive function in elderly subjects.<sup>1</sup> The results showed a dramatic increase in cognitive function on a variety of cognitive function tests after 1 y of supplementation in healthy elderly people. We were surprised to see the Mini-Mental State Examination (MMSE) score in this healthy group increasing from a mean of 18 ( $\pm 3$ ) to 28 ( $\pm 4$ ) in the supplement group (Table II). A MMSE score of less than 26 would conventionally be classified as indicative of mild cognitive impairment, and one less than 22 would be indicative of significant cognitive impairment.<sup>2</sup> Therefore, some of this group must have been demented according to conventional criteria, but Chandra stated that "none suffered from any form of psychiatric illness or dementia" (p. 709). If the conventional screening test of the MMSE was not used to screen for dementia, how was this diagnosis excluded?

The effect of supplementation on the initially low MMSE scores was dramatic and implied a jump from highly cognitively impaired to normal cognitive function. This is a significantly larger treatment effect than, e.g., a pharmacologic treatment for Alzheimer's disease, donepezil, which improved the MMSE by 1.7 points (95% confidence interval:  $-2.59$  to  $-0.82$ ) when compared with placebo.<sup>3</sup> The treatment effect of supplementation, i.e., increasing the MMSE by 10 points (Table II), is remarkable, at almost six times the effect size for a drug designed to target cognitive decline.

Further, the results reported in Table II are quoted as mean  $\pm$  standard error of the mean. If these results are used to calculate standard deviations and thus 95% confidence intervals, the 95% confidence intervals are extremely wide, even extending the possible results of the test (e.g., MMSE placebo at 0 mo:  $-6.6$  to  $48.6$ ). Are these in fact mean  $\pm$  standard deviation?

These points need to be clarified before concluding that "supplements for all elderly subjects should significantly improve cognition and thus quality of life and the ability to perform activities of daily living."

**Susan D. Shenkin, MBChB**  
**Martha C. Whiteman, PhD**  
**Alison Pattie, BSc**  
**Ian J. Deary, PhD**  
*Department of Psychology*  
*University of Edinburgh*  
*Edinburgh, United Kingdom*

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Correspondence to: Susan D. Shenkin, MD, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. E-mail: susan.shenkin@ed.ac.uk

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## Response to Comments of Shenkin et al.

*To the Editor:* Thank you for the opportunity to respond to the valuable comments of Shenkin et al. on our recent paper.<sup>1</sup> We also were pleasantly surprised with significant changes in various cognitive function tests in apparently healthy individuals 65 years and older. In addition to the adapted Mini-Mental State Examination scoring, we relied on clinical assessment including the Clinical Global Impression,<sup>2</sup> Clinical Interview-Based Impression,<sup>3</sup> Alzheimer Disease Assessment,<sup>4</sup> and information from informants and caregivers. There was no clinical evidence of dementia in any of the study subjects. A dichotomy between Mini-Mental State Examination and clinical assessment and cognitive test scores is recognized.<sup>5</sup>

The comparison between the effects of a pharmacologic agent such as donepezil with a known mechanism of action, namely selective inhibition of cholinesterase, and the effects of various micronutrients that influence a variety of enzymatic and metabolic pathways is inappropriate. A few substances, some with recognized antioxidant properties, have been documented to improve the clinical condition of patients with Alzheimer's disease, slow the loss of ability to perform activities of daily living, and delay institutional placement.<sup>5,6</sup> In the placebo-controlled trial of  $\alpha$ -tocopherol (vitamin E) and selegiline,<sup>5</sup> substances with antioxidant properties, there was a slower progression of disease and a longer interval in reaching defined endpoints of worse clinical state in treated subjects compared with placebo controls *but there was no difference in the groups on the Cognitive subscale of the Alzheimer Disease Assessment Scale or any other cognitive test score*. Several physiologic benefits are known to accrue from the use of moderate doses of nutrient supplements even among subjects who have no clinical or biochemical evidence of "deficiency."<sup>7,8</sup>

In another scenario, the administration of antiallergic pharmaceutical medications is not expected to prevent atopic disease, whereas nutritional manipulation such as dietary precautions by the nursing mother and decreased neonatal exposure of the infant to common allergenic foods does reduce the incidence and severity of allergic disease in high-risk infants and the general population of newborns.<sup>9,10</sup>

There was a typographic error in the legends to the tables in our paper. The results shown were means and standard *deviations*.

The many beneficial effects of micronutrient supplements in modest amounts in persons 50 y and older are now well established on the basis of many controlled studies and clinical observations. The subjective experiences of thousands of individuals who have used the vitamin and trace element supplements assessed in our

Correspondence to: R. K. Chandra, MD, Department of Pediatrics and Medicine, Janeway Child Health Center, Memorial University of Newfoundland, St. Johns, Newfoundland A1A 1R8, Canada. E-mail: rchandra@morgan.ucs.mun.ca

studies support the results of the objective controlled trials by others and us.<sup>11</sup>

**R. K. Chandra, OC, MD, FRCPC, MACP**  
*Crans-sur-Sierre, Switzerland*

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