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Corresponding Author: Prof. David Smith, DPhil

Corresponding Author's Institution: University of Oxford

First Author: David Smith, DPhil

Order of Authors: David Smith, DPhil; Helga Refsum, MD; Robin Jacoby, MD

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Alzheimer's disease: early-stage disease-modifying treatment is feasible

A. David Smith FMedSci,

Oxford Project to Investigate Memory and Ageing (OPTIMA), Department of Pharmacology,
University of Oxford, Mansfield Rd., Oxford OX1 3QT, UK

Helga Refsum MD,

Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, 0316 Oslo,
Norway

Robin Jacoby MD,

Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

Corresponding author:

Prof A. David Smith: david.smith@pharm.ox.ac.uk

Tel +44-7768-611-472

The Lancet Neurology Commission is to be congratulated on the report ‘Defeating Alzheimer’s disease and other dementias’¹ that provides a rich resource for researchers and policy-makers. The judgements in the report are in general balanced and based upon a thorough assessment of the field. However, we would like to comment on some aspects. First, the report mentions 15 times the concept of a ‘cure’ for Alzheimer’s disease (AD), without specifying what this ‘cure’ is expected to achieve. AD, once clinically expressed, is associated with the loss of so much brain tissue that it is hard to imagine how the tissue can be replaced, let alone the memories and other cognitive functions. ‘Prevention’ of AD, a realistic target, is on the other hand mentioned more than 70 times. Unfortunately, research into prevention is poorly supported: less than 1% of total UK Research Council funding on dementia research since 2008 has been on prevention. Second, the report emphasizes the need ‘to develop safe and effective disease-modifying treatments’ (page 455) but states ‘disease-modifying treatments are not available at present’ (page 457). The report does not acknowledge that a disease-modifying treatment has already been reported for the subgroup of people with Mild Cognitive Impairment (MCI) with elevated plasma homocysteine.²⁻⁴ In citing this clinical trial (VITACOG), the report incorrectly states (page 505) ‘no significant benefit with respect to.... the rate of brain atrophy was found for the whole group’. The fact is that an average and highly significant 30% reduction in the rate of atrophy was observed in those treated with B vitamins.² Furthermore, the analysis based upon the baseline concentration of homocysteine was not post hoc (as stated) but was pre-specified based on the assumption that B vitamin treatment would be most effective in those with low B vitamin status. Subjects with homocysteine above the median responded to B vitamins with up to a 53% reduction in global brain atrophy rate,² and with a seven-fold reduction in atrophy rate of brain regions known to be vulnerable to AD.⁴ Furthermore, the same subjects experienced a marked slowing of cognitive and clinical decline³. Bayesian network analysis showed that

the lowering of plasma homocysteine by B vitamin treatment was causally linked to the slowing of regional brain atrophy and that that, in turn, was linked to the slowing of cognitive decline.⁴ This modification of the disease process in MCI was further enhanced in those with a good baseline status of omega-3 fatty acids.⁵

The VITACOG trial provides physical evidence from brain volume changes, as well as neuropsychological and clinical evidence, that the disease process in MCI can be modified. There is an urgent need to carry out further RCTs to see if B vitamin treatment of those with MCI and elevated homocysteine will slow, or prevent, the conversion to dementia. But, as the report points out (page 507), ‘the absence of a strong commercial interest in the development of non-pharmacological interventions has meant that funding for RCTs is difficult to obtain.’ That has, indeed, been our experience.

Declaration of interests. Dr Smith is named as inventor on patents US6008221 and US6127370 with royalties paid by PamLab to University of Oxford; Drs Refsum and Smith are named as inventors on two patent applications pending PCT/GB2010/051557 and WO2015/140545 A1.

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