Mendonca N, Granic A, Mathers JC, Martin-Ruiz C, Wesnes KA, Seal CJ, Jagger C, Hill TR.

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Journal of the American Medical Directors Association 2017, 18(10), 895-896

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DOI link to article:

<https://doi.org/10.1016/j.jamda.2017.07.010>

Date deposited:

20/12/2017

Embargo release date:

23 August 2018

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Homocysteine, tryptophan and cognition in the very old

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We thank Dr Gostner and colleagues for their comments on our paper “One-Carbon Metabolism Biomarkers and Cognitive Decline in the Very Old: The Newcastle 85+ Study” ⁽¹⁾. In their letter to the Editor, Dr Gostner and colleagues highlight the complexity of the underlying metabolic processes and conclude that “The question arises whether the inclusion of tryptophan metabolism measurements would allow better conclusions about relevant biochemical pathways and neurotransmitters in the development of cognitive decline in the elderly than homocysteine and 1-carbon (1-C) metabolism can do, because alterations of the latter metabolic pathways are most probably secondary to immune activation and inflammation.” ⁽²⁾. While further measurements would be beneficial in elucidating the link between 1-C metabolism and cognition, we think that it is unlikely that immune activation and inflammation are the main causes for altered 1-C metabolism.

Convincing data for the association between B vitamins, homocysteine and cognition is provided by the VITACOG studies ⁽³⁾ which showed that the rate of brain atrophy was 53% slower in those supplemented with vitamin B₆, vitamin B₁₂ and folic acid but only in those with raised total homocysteine (tHcy) concentrations (>13 mmol/L) at baseline ⁽³⁾. In a following study from this group, the cerebral atrophy was pinpointed to the grey matter regions (including the medial temporal lobe) which are specifically susceptible to Alzheimer’s disease ⁽⁴⁾. It was concluded that the decline in brain atrophy in older adults with mild cognitive impairment could be slowed through normalising tHcy concentrations by B vitamin supplementation ^(3,4).

Dr Gostner and colleagues draw attention to the potential importance of tryptophan and its metabolites in the development of cognitive impairment. In the Newcastle 85+ Study, we did not measure concentrations of tryptophan or its metabolites (e.g. kynurenine) ⁽⁵⁾. However, we have explored the effects of diet ^(6,7), the sole source of tryptophan in humans, on cognitive function in the Newcastle 85+ Study ⁽⁸⁾. Granic A *et al* found that dietary patterns (DP) high in red meat (including processed red meats), potato and gravy (DP1), or butter (DP3) were associated with poor cognition but not with the rate of cognitive decline in very old adults ⁽⁸⁾. Participants with DP1 and DP3 had worse Standardized Mini-Mental State Examination (SMMSE) scores ($\beta = 0.09$, $P = 0.01$ and $\beta = 0.08$, $P = 0.02$, respectively) than those with a low meat diet (DP2) after adjustment for key confounders. Participants in DP1 and DP3 also had worse reaction time ($\beta = 0.04$, $P = 0.002$ and $\beta =$

0.03, $P = 0.03$, respectively) and focused attention ($\beta = 0.02$, $P = 0.01$ and $\beta = 0.02$, $P = 0.03$, respectively) ⁽⁸⁾.

As Gostner JM *et al* mentioned, inflammation is of great relevance to neurodegeneration and cognitive function ⁽²⁾. Using the Newcastle 85+ Study, Granic A *et al* derived inflammatory biomarker profiles by principal component analysis (PCA) explaining 70% of the total variance in seven baseline biomarkers (basal and stimulated interleukin-6, basal tumour necrosis factor α , tHcy, high sensitivity c-reactive protein and albumin) ⁽⁹⁾. Using data from the Newcastle 85+ Study, we are planning to investigate the relationship between the inflammatory biomarker profiles and cognitive function in the very old. In addition, in the final growth models used in our paper ⁽¹⁾ we explored the relationship between tHcy concentrations and global cognition (SMMSE) and attention (assessed by CDR System) ⁽¹⁾, and further adjusted for high-sensitivity C-Reactive Protein (hs-CRP). Inclusion of this inflammatory biomarker (hs-CRP) did not change the results for the SMMSE or for scores from the CDR System reflecting focussed attention, sustained attention and fluctuations in attention. This suggests that the inverse association between tHcy and cognition that we observed in the very old may be independent of inflammation. However, we reserve our conclusions about this relationship until the investigation of the associations between inflammatory biomarker profiles and cognitive decline in the Newcastle 85+ Study is completed.

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