

Supplementary Online Content

Hooshmand B, Refsum H, Smith AD, et al. Association of methionine to homocysteine status with brain magnetic resonance imaging measures and risk of dementia. *JAMA Psychiatry*. Published online July 24, 2019. doi:10.1001/jamapsychiatry.2019.1694

eAppendix. Methods

eTable 1. Hazard ratios (HR) and 95% confidence intervals (in brackets) examining the associations of methionine (as quartiles, with quartile 1 as reference) with incident dementia after adjusting for hours of fasting, homocysteine, cysteine, vitamin B12, and folate

eTable 2. Hazard ratios (HR) and 95% confidence intervals (in brackets) examining the associations of methionine/homocysteine ratio (as quartiles, with quartile 1 as reference) with incident dementia after adjusting for hours of fasting, homocysteine, cysteine, vitamin B12, and folate

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Brain Imaging

Participants were examined on a 1.5T MR scanner (Philips Intera, Netherlands) and the protocol has been described elsewhere (Hooshmand et al, JAMA Psychiatry 2016; 73(6):606-613). Total gray matter volume (GMV) and white matter volume (WMV) were calculated after automatic segmentation of the T1 images in native space using SPM12b software (Statistical Parametric Mapping, <https://www.fil.ion.ucl.ac.uk/spm/>), implemented in Matlab, using the unified segmentation approach (Ashburner & Friston. Neuroimage. 2005 Jul 1;26(3):839-51). Total brain tissue volume (TBT) was obtained by adding GMV and WMV. Total intracranial volume (TIV) was finally calculated by adding the volumes of TBT and cerebrospinal fluid (CSF). All segmentations were carefully checked visually for quality control. TBT, GMV, and WMV were expressed in proportion to TIV to correct for headsize and multiplied by 100.

To measure global WMH volumes, all white matter hyperintensities were manually drawn on FLAIR images by a single rater and further interpolated on the corresponding T1-weighted images to compensate for the gap between slices in FLAIR (for detail about the procedure and intra-rater reliability, see Köhncke et al., Neurobiol Aging 41:173-86.2016). Total WMH volumes were divided by subjects' TBT prior to hypothesis testing.

eTable 1. Hazard ratios (HR) and 95% confidence intervals (in brackets) examining the associations of methionine (as quartiles, with quartile 1 as reference) with incident dementia after adjustment for hours of fasting, homocysteine, cysteine, vitamin B12, and folate

	Quartile 2	Quartile 3	Quartile 4
Methionine Multiadjusted HR ¹	0.80 (0.57 – 1.13)	0.58 (0.39 – 0.86) ³	0.54 (0.36 - 0.81) ³
Additionally adjusted for hours of fasting	0.84 (0.59 – 1.20)	0.66 (0.44 – 0.98) ³	0.60 (0.40 -0.91) ³
Additionally adjusting for homocysteine	0.83 (0.59 – 1.17)	0.59 (0.40 – 0.87) ³	0.55 (0.37 – 0.83) ³
Additionally adjusting for cysteine	0.82 (0.58 – 1.15)	0.60 (0.40 – 0.88) ³	0.54 (0.36 – 0.82) ³
Additionally adjusted for vitamin B12	0.80 (0.57 – 1.23)	0.61 (0.41 – 0.91) ³	0.55 (0.37 – 0.83) ³
Additionally adjusted for folate	0.80 (0.57 – 1.12)	0.58 (0.39 – 0.86) ³	0.55 (0.37 – 0.83) ³

Methionine quartiles were: $\leq 19.5\mu\text{mol/L}$ (quartile 1), $19.6\text{-}22.9\mu\text{mol/L}$ (quartile 2), $23.0\text{-}26.8\mu\text{mol/L}$ (quartile 3), and $>26.8\mu\text{mol/L}$ (quartile 4).

¹The multiadjusted model was adjusted for age, sex, education, creatinine, SBP, use of vitamins, albumin, smoking, and history of cardiovascular conditions, and stroke. ³ $p < 0.05$; ⁴ $P < 0.1$

eTable 2. Hazard ratios (HR) and 95% confidence intervals (in brackets) examining the associations of methionine/homocysteine ratio (as quartiles, with quartile 1 as reference) with incident dementia after adjustment for hours of fasting, homocysteine, cysteine, vitamin B12, and folate

	Quartile 2	Quartile 3	Quartile 4
Methionine/homocysteine ratio Multiadjusted HR ¹	0.77 (0.55 – 1.09)	0.53 (0.35 – 0.80) ³	0.44 (0.27 – 0.71) ³
Additionally adjusted for hours of fasting	0.78 (0.55 – 1.12)	0.57 (0.37 – 0.86)	0.48 (0.29 – 0.78)
Additionally adjusting for homocysteine	0.71 (0.49 – 1.05) ⁴	0.48 (0.31 – 0.76) ³	0.39 (0.23 – 0.66) ³
Additionally adjusting for Cysteine	0.79 (0.56 – 1.12)	0.55 (0.37 – 0.84) ³	0.46 (0.28 – 0.74) ³
Additionally adjusted for vitamin B12	0.78 (0.55 – 1.11)	0.54 (0.36 – 0.82) ³	0.44 (0.27 – 0.72) ³
Additionally adjusted for folate	0.76(0.53 – 1.08)	0.52 (0.34 – 0.79) ³	0.42 (0.26 – 0.69) ³

Methionine quartiles were: ≤ 1.35 (quartile 1), 1.36-1.79 (quartile 2), 1.80-2.35 (quartile 3), and >2.35 (quartile 4).

¹The multiadjusted model was adjusted for age, sex, education, creatinine, SBP, use of vitamins, albumin, smoking, and history of cardiovascular conditions, and stroke. ³p < 0.05; ⁴P < 0.1