Original Study

One-Carbon Metabolism Biomarkers and Cognitive Decline in the Very Old: The Newcastle 85+ Study

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ABSTRACT

Objectives: Although the biological rationale for the association between folate, vitamin B12, and homocysteine with cognitive function seems plausible, conflicting results have been reported. This study aimed to determine the associations between 1-carbon (1-C) metabolism biomarkers (folate, vitamin B12, and homocysteine), and cognitive impairment at baseline and the rate of cognitive decline over 5 years in the very old.

Design: The Newcastle 85+ Study was a prospective longitudinal study of people 85 years old and followed over 5 years in Northeast England.

Setting: Community-dwelling and institutionalized.

Participants: The analytical sample included 765 very old participants with 1-C metabolism biomarkers and cognitive measures.

Measurements: Global cognition was measured by the Standardized Mini-Mental State Examination (SMMSE) at baseline, and at 3 and 5 years of follow-up and, attention-specific cognition with the Cognitive Drug Research (CDR) System at baseline, and at 1.5 and 3.0 years of follow-up. Baseline red blood cell folate (RBC folate), plasma vitamin B12, and total homocysteine (tHcy) concentrations were determined by immunoassay. Linear mixed models were used to estimate the associations between quartiles of 1-C metabolism biomarkers and cognition over 3 (CDR) and 5 years (SMMSE).

Results: Compared with participants in the lowest quartile of RBC folate concentrations (<612 nmol/L), those in the highest quartile of RBC folate concentrations (>1280 nmol/L) had 1 more point on the SMMSE at baseline ($\beta = +1.02$, SE $= 0.43$, $P = .02$). Those in quartile 4 of tHcy (>21.4 μmol/L) had 1 point less in the SMMSE at baseline than those in the lowest quartile (<13.5 μmol/L) ($\beta = -1.05$, SE $= 0.46$, $P = .02$). Plasma vitamin B12 was not predictive of global or attention-specific cognition at baseline and at follow-up. None of the 1-C metabolism biomarkers except tHcy was associated with the rate of decline in attention scores over 3 years.

Conclusion: RBC folate and tHcy, but not plasma vitamin B12, were associated with better global cognition in the very old at baseline but were not predictive of rate of decline over 5 years.

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There are now 46.8 million people with dementia worldwide, and that number is predicted to reach 74.7 million by 2030.[1] The Cognitive Function and Ageing Study (CFAS) II estimated that there were 670,000 older adults with dementia in 2011 in England alone.[2] Despite some evidence of reduction in the prevalence and incidence of dementia,[2,3] it is predicted that cases of dementia will increase primarily for the following reasons: (1) dementia incidence doubles every 6.3 years after 60 years old[1]; and (2) the population is aging worldwide predominantly because of the rise in the numbers of the very old (85 years and older), the fastest growing age segment in the United Kingdom and most Western societies.[4] Dementia is one of the most important predictors of disability and poses a major societal challenge.[5] Because cognitive decline and dementia affect quality of life detrimentally and are currently not treatable, research priorities have focused on preventing or delaying the onset of dementia through modifiable risk factors, such as nutrition.[6]

Folate and vitamin B12 are B vitamins that are central to 1-carbon (1-C) metabolism. Inadequate or aberrant 1-C metabolism may be associated with cognitive function through mechanisms such as hyperhomocysteinemia[7]; reduced synthesis of neurotransmitters, phosphatidylcholine, and pyrimidines[8]; altered DNA methylation patterns[9]; and reduced fatty acid synthesis and incorporation of odd chain fatty acids into the myelin sheath.[10]

Although the biological rationale for associations between folate, vitamin B12, and homocysteine with cognitive function seem plausible, conflicting results have been reported. Folate, vitamin B12, and homocysteine have been associated with cognitive decline in some longitudinal studies,[11–13] but not all,[14–17] in some randomized controlled trials (RCTs),[18–20] for one vitamin but not the other, or only for certain cognitive domains. Insufficient follow-up time, small sample size, participants' age at recruitment, and different cognitive tests used are frequently reported reasons for the conflicting results. Furthermore, studies targeting the very old are lacking. We hypothesized that higher red blood cell (RBC) folate and plasma vitamin B12 concentrations would be associated with better cognitive performance and slower rate of cognitive decline, primarily through homocysteine-lowering effects. This study aimed to determine the associations between RBC folate, plasma vitamin B12, and total homocysteine (tHcy) concentrations at baseline, and cognitive impairment and the rate of cognitive decline in global and attention-specific cognition over 5 years in a large population of the very old who participated in the Newcastle 85+ Study.

Methods

Participants

Briefly, the Newcastle 85+ Study is a longitudinal study of health trajectories and outcomes in the very old that approached virtually all people turning 85 in 2006 (born in 1921) in North East England. The recruited cohort was broadly sociodemographically representative of the general UK population and, included institutionalized and cognitively impaired very old adults,[21] 2 commonly excluded groups. Data were collected on multidimensional health aspects and general practice medical records were reviewed at baseline (2006/2007), 18 months (1.5 years), 36 months (3 years), and 60 months later (5 years)[22] (Figure A1). Further information is reported elsewhere[21–24] (for study questionnaires visit http://research.ncl.ac.uk/85plus).

Biomarkers of 1-C Metabolism

Forty milliliters of blood were drawn from the antecubital vein between 7:00 and 10:30 AM after an overnight fast, and 95% of the samples reached the laboratory within 1 hour. Both RBC folate and plasma vitamin B12 were quantified by chemiluminescence (Microparticle Immunoassay on Abbott ARCHITECT analyzer [Abbot Park, IL]) and tHcy by an Abbot IMx immunoassay at baseline.[25]

Cognitive Assessment

The Standardized Mini-Mental State Examination (SMMSE) was used to assess global cognitive status at baseline and 3- (36 months) and 5-year (60 months) follow-up (Figure A1). The SMMSE is a short, standardized screening test for cognitive impairment in older adults that ranks global cognitive function from 0 to 30. Individuals with SMMSE scores ≥26 were considered as healthy and ≤25 as cognitively impaired.[26] Three automated tests of attention from the Cognitive Drug Research (CDR) System were used to assess cognition at baseline and again after 1.5 (18 months) and 3.0 years (36 months) (Figure A1). The tests were simple reaction time (SRT), which assesses focused attention and concentration; choice reaction time (CRT), which assessed similar abilities in addition to information processing and decision making; and the digit vigilance task (DVT) that assesses the ability to sustain attention.[27] Using the measures of speed and accuracy from the tasks, 3 validated composite measures were derived: power of attention (PoA), the sum of 3 speed scores that reflects the ability to focus attention and the intensity of concentration; reaction time variability (RTV), which is a sum of the coefficients of variance of the reaction time scores and reflects variations in attention during the tasks; and continuity of attention (CoA), which combines the accuracy scores from CRT and DVT and reflects the ability to sustain attention.[28,29] All 3 of these composite scores have been validated previously.[30,31] Higher scores in the SMMSE and the CoA, and lower scores for the PoA and RTV measures reflect superior performance.

Other Confounders

Whole-blood DNA was extracted fusing a QiaGEN (Hilden, Germany) Amp Maxi DNA Purification Kit and the gene encoding apolipoprotein E (APOE) genotyped for common polymorphisms at rs429358 and rs7412 (to provide information on zygosity at ε2, ε3, and ε4 alleles) by Illumina Omni (San Diego, CA) genotyping arrays.[25] Multidimensional health questionnaires recorded sex, current housing, years of full-time education, depression (Geriatric Depression Scale), physical activity, supplement use,[32] alcohol intake (confirmed by 2 × 24-hour multiple pass recalls[33]), and smoking status. Medical records held by the general practitioner were reviewed for diagnosed dementia/Alzheimer disease, diabetes type 1 and 2, hypertension, and history of cardiovascular disease (including angina, myocardial infarction, coronary angioplasty, coronary artery bypass graft, atrial fibrillation, atrial flutter, heart failure, pacemaker use, stroke, transient ischemic attack, and carotid endarterectomy). Weight and height were measured and used to calculate body mass index (BMI). Renal impairment was determined by the chronic kidney disease epidemiology collaboration (CKD-EPI) guidelines using sex, ethnicity, serum creatinine, and age.[34]

Statistical Analysis

Statistical analyses were conducted using SPSS v22.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Normality was assessed with the Shapiro-Wilk test and confirmed with histograms and Q-Q plots. Linearity assumptions were tested with residuals versus predicted values plots. Multicollinearity of confounders was assessed with variance inflation factor, tolerance, and eigenvalues. Normally distributed continuous values are presented as means and SDs, and non-Gaussian−distributed variables as medians and interquartile ranges (IQRs). Categorical data are presented as percentages (with corresponding sample size). Differences between quartiles of RBC folate, plasma vitamin B12, and tHcy were assessed with χ^2 test for