Cognitive Function in an Elderly Population: Interaction Between Vitamin B_{12} Status, Depression, and Apolipoprotein E ε4: The Hordaland Homocysteine Study

Anna Vogiatzoglou, DPhil, A. David Smith, DPhil, Eha Nurk, PhD, Christian A. Drevon, MD, PhD, Per M. Ueland, MD, PhD, Stein E. Vollset, MD, DrPH, Harald A. Nygaard, MD, PhD, Knut Engedal, MD, PhD, Grethe S. Tell, PhD, and Helga Refsum, MD, PhD

Objective: To investigate the cross-sectional relation between metabolic markers of vitamin B_{12} status and cognitive performance, and possible effect modification by the presence of depression and apolipoprotein E (ApoE) ε4. **Methods:** This is a population-based study of 1935 participants, aged 71 to 74 years, from Norway. Participants were administered a cognitive test battery, and vitamin B_{12} status was assessed by measurements of plasma vitamin B_{12}, holotranscobalamin (holoTC), methylmalonic acid (MMA), and total homocysteine. **Results:** The geometric mean (95% confidence interval) for vitamin B_{12} was 348 pM (341–354), whereas 5.9% of participants had vitamin B_{12} levels lower than 200 pM. In linear regression analyses, holoTC ($p = .039$) and the holoTC/vitamin B_{12} ratio ($p = .013$) were positively related, whereas MMA ($p = .010$) was inversely related, to global cognition, after adjustment for sex, education, ApoE status, plasma creatinine, and history of diabetes, cardiovascular disease, hypertension, and depression. Among those positive for ApoE ε4, but not among those without the ε4 allele, plasma vitamin B_{12} was positively associated with global cognition ($p = .015$), whereas MMA was inversely related to global cognition ($p = .036$) and executive function ($p = .014$). In participants with depression, MMA was inversely associated with global cognition ($p < .001$) and episodic memory ($p = .001$). **Conclusions:** Among the well-nourished elderly, low vitamin B_{12} status is associated with cognitive deficit, particularly in those with the ApoE ε4 allele or with depression. **Key words:** plasma vitamin B_{12} status, methylmalonic acid, holotranscobalamin, depression, apolipoprotein E ε4, cognitive performance.

ApoE = apolipoprotein E; **MMA** = methylmalonic acid; **tHcy** = total homocysteine; **holoTC** = holotranscobalamin; **TC** = transcobalamin; **m-MMSE** = modified version of the Mini-Mental State Examination; **KOLT** = Kendrick Object Learning Test; **m-BD** = modified version of Block Design; **m-DST** = modified version of the Digit Symbol Test; **COWAT** = abridged version (S-task) of the Controlled Oral Word Association Test; **TMT-A** = part A of the Trail Making Test; **HADS-D** = Hospital Anxiety and Depression Scale, depression subscale.

INTRODUCTION

Progression of cognitive impairment and development of dementia are complex processes involving several genes and synergistic interactions with and between environmental factors (1). Vitamin B_{12} deficiency has been suggested as an important modifiable factor, and there are reports that its association with cognitive decline may depend on the presence of genetic polymorphisms, such as apolipoprotein E (ApoE) ε4 (2,3), and coexisting depression (4).

Subnormal plasma levels of vitamin B_{12} are prevalent among the elderly (5,6) and may be associated with megaloblastic anemia, neurologic disorders (such as neuropathy, myelopathy, dementia, depression, and brain atrophy), and cerebrovascular disease (7–11). Several studies have reported on the benefits of high levels of vitamin B_{12} on cognition or on associations between low vitamin B_{12} levels and cognitive deficit among community-dwelling elderly people and patients with cognitive impairment, whereas others have yielded null results (12,13). The results of these studies are inconclusive, possibly because of differences in the diagnosis of vitamin B_{12} deficiency and in the assessment of cognitive function, but perhaps also because other synergistic factors have not been identified.

The standard clinical screening test for the diagnosis of vitamin B_{12} deficiency—measurement of plasma or serum vitamin B_{12}—has low diagnostic accuracy (14), whereas plasma levels of total homocysteine (tHcy) and methylmalonic acid (MMA) are considered to be more sensitive markers of vitamin B_{12} status (14,15). Holotranscobalamin (holoTC)—the portion of vitamin B_{12} bound to the transport protein transcobalamin (TC)—and the related TC saturation (the fraction of total TC present as holoTC) represent the biologically active fraction of total vitamin B_{12} and have been proposed as potentially useful indicators of vitamin B_{12} status (16,17). A recent study (4) suggested that the percentage of total vitamin B_{12} bound to TC (holoTC/B_{12} ratio) may provide important information about the availability of vitamin B_{12} for delivery to the tissues and may possibly provide a sensitive measure of vitamin B_{12} status. These markers, used in conjunction with total vitamin B_{12}, may allow for better discrimination of vitamin B_{12} status than total vitamin B_{12} alone (18,19).

From the OPTIMA (A.V., A.D.S., H.R.), Department of Pharmacology, University of Oxford, Oxford, UK; Department of Surveillance and Evaluation (E.N.), National Institute for Health Development, Tallinn, Estonia; Institute of Basic Medical Sciences (A.V., E.N., C.A.D., H.R.), Department of Nutrition, Faculty of Medicine, University of Oslo, Oslo; Section for Pharmacology (P.M.U.), Institute of Medicine, University of Bergen and Haukeland Hospital, Bergen; Department of Public Health and Primary Health Care (S.E.V., H.A.N., G.S.T.), University of Bergen, Bergen; NKS Olaviken Hospital for Old Age Psychiatry (H.A.N.), Erdal; and Norwegian Center for Dementia Research (K.E.), Department of Geriatric Medicine, Ullevål University Hospital, Oslo, Norway.

Address correspondence and reprint requests to Anna Vogiatzoglou, DPhil, Department of Food and Nutritional Sciences, University of Reading, Whiteknights, PO Box 226, Reading RG6 6AP, UK. E-mail: a.vogiatzoglou@reading.ac.uk

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ApoE is involved in the regulation and transport of lipids and is believed to have regulatory properties over the deposition and formation of amyloid plaques and neurofibrillary tangles, both hallmarks of Alzheimer's disease (20). The presence of the ApoE ε4 allele is the major genetic risk factor associated with an increased risk of dementia (21–25). Furthermore, individuals with the ApoE ε4 genotype are more vulnerable to the influence of other nongenetic risks for dementia (26).

Depression may accelerate cognitive decline and is believed to have an additive effect on adverse outcomes for physical health, functional status, and mortality (27). Low vitamin B_{12} status has been found in studies of patients with depression (9,28–32), and an association between depression and low vitamin B_{12} has been found in the general population (33–35). Although limited, there is evidence that the associations between plasma vitamin B_{12} or markers of vitamin B_{12} status and cognitive function test scores (4,36–38) are stronger in patients with depression than in patients without depression.

The aim of this cross-sectional study on approximately 2000 community-dwelling elderly people was to assess the associations of several markers of plasma vitamin B_{12} status with specific cognitive domains. In particular, we wished to see if the presence of two factors already shown to influence cognition in this population, ApoE ε4 allele (39) and depressive symptoms (40), might modulate the association with vitamin B_{12}.

METHODS

Study Participants

The Hordaland Health Study was conducted from 1997 to 1999 as collaboration between the National Health Screening Service, the University of Bergen, and local health services (41). All attending participants from the city of Bergen who were born in the period 1925 to 1927 and attended the Hordaland Homocysteine Study in 1992 to 1993 were invited to participate in cognitive testing (41). The present study population includes the group of 1967 participants who underwent cognitive examination. Those who reported having injections of vitamin B_{12} (n = 32) were excluded, leaving 1935 participants for analysis. The study protocol was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants gave their written informed consent to participate in the study.

Health Examination and Analytic Procedures

Participants underwent a brief health examination and provided a nonfasting blood sample. Information on diet, life-style, and medical history was collected via self-administered questionnaires (41). The health examination included measurements of height, weight, and blood pressure. Nonfasting plasma samples were collected into tubes containing EDTA and stored at −80°C for biochemical analyses. Plasma tHcy was determined by automated high-performance liquid chromatography with fluorescence detection (42). The concentrations of plasma folate and vitamin B_{12} were measured by *Lactobacillus casei* (43) and *Lactobacillus leichmannii* microbiological assays (44), respectively. Plasma MMA was analyzed by using a modified gas liquid chromatography–mass spectrometry method based on ethylchloroformate derivatization (45). Plasma holoTC was measured by a microbiological assay developed for cobalamin estimation (17) that was adapted to a microtiter plate format and carried out by a robotic workstation (Perkin-Elmer MultiProbe11). Total TC was measured as holoTC after the binding sites had been saturated with cyanocobalamin (17). Plasma creatinine was measured by a modified liquid chromatography–mass spectrometry procedure (46). ApoE genotypes were determined using a one-stage polymerase chain reaction method (47).

Assessment of Cognitive and Mental Status

Cognitive testing was performed at the study location by specially trained nurses. The six cognitive tests included the following: a modified version of the Mini-Mental State Examination (m-MMSE; global cognition), the Kendrick Object Learning Test (KOLT; episodic memory), a modified version of the Digit Symbol Test (m-DST; perceptual speed), the abridged version (S-task) of the Controlled Oral Word Association Test (COWAT; access to semantic memory), part A of the Trail Making Test (TMT-A; executive function), and a modified version of Block Design (m-BD; visuospatial skills). All cognitive tests have been previously described in detail (48). In all tests, except for TMT-A, a lower score indicates poorer performance. Levels of anxiety and depression symptoms were assessed by the seven-item Hospital Anxiety and Depression Scale, anxiety subscale, and the seven-item Hospital Anxiety and Depression Scale, depression subscale (HADS-D), respectively (49). In this study, only HADS-D score was used as it is more relevant to cognitive function. All participants completed at least one cognitive test; 48 individuals were not assessed for depression. The observations for which the scores of the various cognitive tests were missing were less than 1% of the sample; in all participants, when an observation did not include data on the cognitive score in question, that observation was not included in the relevant analysis.

Statistical Analyses

All calculations were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). Results are expressed as means and 95% confidence intervals. The distributions of plasma markers of vitamin B_{12} status were markedly skewed; log-transformed data were used in all analyses and backtransformed for the presentation of geometric means and 95% confidence intervals. For comparison between groups, χ^2 test was used. Cutoff points for poor cognitive test scores were set at about the 10th percentile of the cognitive test score, except for TMT-A, for which the 90th percentile was used (48). As in a previous report on this population, a HADS-D score higher than 7 is suggestive of depression (40). Pearson correlation coefficients were used to assess simple correlations between plasma variables and cognitive test scores.

Multiple linear regression analyses were used to describe the associations between plasma vitamin B_{12} markers (independent variables) and cognitive tests (dependent variables). Adjustment variables included sex (male or female), years of education (elementary school or <10 years, technical or high school, or college or ≥13 years), ApoE status (ApoE ε4–positive or ApoE ε4–negative), diabetes (yes or no), cardiovascular disease (yes or no), depression (continuous), hypertension (yes or no), and plasma creatinine (continuous); for analyses that included tHcy, plasma folate (continuous) was also added in the adjustments. The interaction between vitamin B_{12} markers and ApoE ε4 status or depression score was analyzed and presented separately by adding relevant interaction terms to the above multiple linear regression models. This analysis was performed separately because the multicollinearity introduced by the addition of the interaction terms would make the resulting regression coefficients difficult to interpret. As the range of scores of each cognitive test varies, we reported standardized regression coefficients for meaningful cross-comparisons. To further investigate the presence of a significant interaction between vitamin B_{12} status and the ApoE ε4 genotype or the presence of depression, we used multiple linear regression models for cognitive test scores stratified by ApoE ε4 status and the presence of depression. This was achieved by splitting the sample into two based on the presence of the ApoE ε4 genotype in the first instance and on the presence of depression in the second instance. The resulting models were also adjusted using the aforementioned variables. Body mass index, smoking status, and physical activity were not related to cognitive test scores or markers of vitamin B_{12} status and were excluded from the models because inclusion of these variables in statistical models did not change the results. Log-transformed values were used for both tHcy and folate in linear regression analyses. The participants were homogeneous in age (born 1925–1927); thus, age was not included in the models.

Gaussian generalized additive regression models implemented in S-PLUS version 8.0 (Insightful Corp., Seattle, WA) were used to generate graphic representations of the dose-response relations between plasma vitamin B_{12} status (independent variable) and cognitive test scores (dependent variable), adjusted for covariates included in linear regression models previously described. At

the approximate mean exposure of the independent variable, the model generates a reference value of zero for the dependent variable. Corresponding *p* values were obtained from multiple linear regression analyses.

RESULTS

Selected Characteristics of the Study Population

Selected characteristics of the study population are listed in Table 1. Plasma vitamin B_{12} was within the reference range, and only 5.9% had a vitamin B_{12} level lower than 200 pM, indicating good vitamin B_{12} status in this population. Among the participants, 3.9% had elevated tHcy (>20 μM) and 5.1% had elevated MMA (>0.37 μM), which are the upper reference limits for tHcy and MMA in this population (15,50). Only 1.9% had plasma vitamin B_{12} levels lower than 200 pM combined with MMA values higher than 0.37 μM.

The characteristics of the study population according to cognitive deficit in the six cognitive tests are listed in the supplemental table (Supplemental Digital Content 1, http://links.lww.com/PSYMED/A55). Significant differences between participants with normal scores and participants with poor scores were observed in three tests for participants positive for ApoE ε4, in five tests for participants with 10 or less years of education, and in five tests for participants with symptoms of depression.

TABLE 1. Characteristics of the Study Population

Characteristics	
Age, y[a]	72.5 (72.5–72.6)
Female, n (%)	1042 (53.9)
Current smokers, n (%)	270 (14.0)
Education ≤10 y, n (%)	667 (34.5)
ApoE ε4–positive, n (%)	617 (31.9)
Cognitive and mental tests	
m-MMSE score[a]	11.5 (11.5–11.6)
KOLT score[a]	35.5 (35.1–35.8)
m-DST score[a]	10.4 (10.2–10.6)
COWAT score[a]	15.3 (15.0–15.5)
TMT-A score[a]	55.7 (54.3–57.2)
m-BD score[a]	15.1 (15.0–15.2)
HADS-D score[a]	3.5 (3.3–3.6)
Plasma variables	
Vitamin B_{12}, pM[b]	348 (341–354)
Holotranscobalamin, pM[b]	90 (92–91)
TC saturation, %[b]	9.0 (8.8–9.1)
HoloTC/vitamin B_{12} ratio, %[b]	26.1 (25.6–26.5)
Methylmalonic acid, μM[b]	0.20 (0.19–0.21)
Total homocysteine, μM[b]	11.5 (11.4–11.7)
Creatinine, μM[a]	77 (76–78)

ApoE = apolipoprotein E; m-MMSE = modified version of the Mini-Mental State Examination; KOLT = Kendrick Object Learning Test; m-DST = modified version of the Digit Symbol Test; COWAT = abridged version (S-task) of the Controlled Oral Word Association Test; TMT-A = part A of the Trail Making Test; m-BD = modified version of Block Design; HADS-D = Hospital Anxiety and Depression Scale, depression subscale; TC = transcobalamin; holoTC = holotranscobalamin.

[a] Values are expressed as mean (95% confidence interval).

[b] Values are expressed as geometric mean (95% confidence interval).

TABLE 2. Pearson Correlation Coefficients Between the Six Cognitive Tests and Plasma Variables

	Vitamin B_{12}	HoloTC	TC Saturation	HoloTC/B_{12} Ratio	MMA	tHcy
m-MMSE						
r	0.03	0.04	0.06	0.04	−0.05	−0.05
p	.177	.097	.016	.127	.041	.035
KOLT						
r	−0.03	0.03	0.05	0.07	−0.04	−0.13
p	.291	.225	.030	.006	.070	<.001
m-DST						
r	−0.06	−0.02	0.03	0.04	0.03	−0.08
p	.007	.496	.155	.105	.253	.001
COWAT						
r	−0.05	−0.01	0.02	0.03	0.01	−0.05
p	.027	.600	.433	.164	.762	.044
TMT-A						
r	0.02	−0.01	−0.02	−0.03	0.03	0.05
p	.497	.771	.404	.7250	.132	.033
m-BD						
r	−0.03	−0.01	0.02	−0.01	−0.01	−0.01
p	.906	.972	.451	.932	.556	.715

HoloTC = holotranscobalamin; TC = transcobalamin; MMA = methylmalonic acid; tHcy = total homocysteine; m-MMSE = modified version of the Mini-Mental State Examination; KOLT = Kendrick Object Learning Test; m-DST = modified version of the Digit Symbol Test; COWAT = abridged version (S-task) of the Controlled Oral Word Association Test; TMT-A = part A of the Trail Making Test; m-BD = modified version of Block Design.

Log-transformed data of the plasma vitamin B_{12} status variables were used in all analyses.

Univariate Associations

Pearson correlation coefficients between the six cognitive tests and plasma variables are presented in Table 2. High plasma MMA was associated with poorer scores in tests of global function (m-MMSE), whereas the holoTC/vitamin B_{12} ratio and TC saturation showed weak positive associations with the episodic memory test (KOLT). A weak inverse association was observed between plasma vitamin B_{12} and semantic memory (COWAT) and perceptual speed (m-DST) test scores. High plasma tHcy was associated with poorer scores in tests of global function (m-MMSE), episodic memory (KOLT), perceptual speed (m-DST), semantic memory (COWAT), and executive function (TMT-A).

Multiple Linear Regression Analyses

Multiple linear regression analysis models for the six cognitive test scores and vitamin B_{12} markers are summarized in Table 3. Table 4 shows the significant associations of the interaction between vitamin B_{12} markers and ApoE ε4 status or depression score with cognitive scores in linear regression models. Table 5 presents multiple linear regression models

TABLE 3. Multiple Linear Regression Models[a]

	Vitamin B_{12}	HoloTC	TC Saturation	HoloTC/B_{12} Ratio	MMA	tHcy[b]
m-MMSE						
R^2	0.046	0.052	0.054	0.056	0.050	0.049
Coefficient	0.083	0.193	0.173	0.318	−0.280	−0.299
Partial *r*	0.02	0.05	0.05	0.07	−0.06	−0.04
p	.420	.039	.073	.013	.010	.107
KOLT						
R^2	0.087	0.085	0.088	0.090	0.090	0.096
Coefficient	−0.937	1.379	1.928	3.261	−2.348	−6.435
Partial *r*	−0.02	0.04	0.05	0.07	−0.05	−0.09
p	.385	.159	.054	.015	.038	.001
m-DST						
R^2	0.163	0.165	0.166	0.167	0.160	0.165
Coefficient	−1.344	−0.092	0.389	1.121	0.623	−1.572
Partial *r*	−0.06	−0.01	0.02	0.04	0.03	−0.04
p	.015	.857	.454	.105	.284	.109
COWAT						
R^2	0.108	0.108	0.108	0.110	0.106	0.110
Coefficient	−1.239	0.170	0.523	1.596	0.156	−1.013
Partial *r*	−0.04	0.01	0.02	0.05	0.01	−0.02
p	.090	.799	.435	.082	.840	.434
TMT-A						
R^2	0.057	0.062	0.066	0.067	0.059	0.063
Coefficient	0.454	−4.290	−2.535	−6.449	8.967	17.773
Partial *r*	0.03	−0.03	−0.02	−0.03	0.05	0.06
p	.917	.281	.534	.235	.051	.022
m-BD						
R^2	0.029	0.029	0.031	0.031	0.030	0.032
Coefficient	−0.152	0.010	0.090	0.264	−0.311	−0.430
Partial *r*	−0.01	0.00	0.01	0.02	−0.03	−0.02
p	.590	.969	.739	.463	.297	.389

HoloTC = holotranscobalamin; TC = transcobalamin; MMA = methylmalonic acid; tHcy = total homocysteine; m-MMSE = modified version of the Mini-Mental State Examination; KOLT = Kendrick Object Learning Test; m-DST = modified version of the Digit Symbol Test; COWAT = abridged version (S-task) of the Controlled Oral Word Association Test; TMT-A = part A of the Trail Making Test; m-BD = modified version of Block Design.

R^2 values are for the entire model, including vitamin B_{12} status measure and all covariates.

Coefficients, partial *r*'s, and their corresponding *p* values are for each vitamin B_{12} status measure within the model.

Sample sizes varied between 1451 and 1601.

Unstandardized regression coefficients are presented.

Partial correlations describe the correlation between the dependent variable (rows) and the independent variable in question (columns) after the effects of the other variables from both the dependent variable and the independent variable were removed.

Log-transformed data of the independent variables were used in all analyses.

[a] Adjusted for sex, apolipoprotein E ε4 status, education, diabetes, hypertension, cardiovascular disease, plasma creatinine, and Hospital Anxiety and Depression Scale, depression subscale score.

[b] Adjusted for sex, apolipoprotein E ε4 status, education, diabetes, hypertension, cardiovascular disease, plasma creatinine, folate, and Hospital Anxiety and Depression Scale, depression subscale score.

for cognitive test scores stratified by ApoE ε4 status and depression score.

In linear regression analysis, plasma MMA, holoTC, and the holoTC/B_{12} ratio were significantly associated with m-MMSE scores after controlling for years of education, sex, ApoE status, history of diabetes and cardiovascular disease, HADS-D score, hypertension, and creatinine, although the associations were relatively weak (Table 3, Fig. 1). As shown in Table 4, there was a significant interaction between vitamin B_{12} and ApoE ε4 on m-MMSE scores. A significant interaction on m-MMSE scores was also observed between depression and vitamin B_{12}, holoTC, and MMA (Table 4). When associations were assessed separately for participants with and without the ApoE ε4 allele, low vitamin B_{12} and high MMA were associated with lower m-MMSE scores in those participants with the ApoE ε4 allele, but not in those without the ApoE ε4 allele (Table 5, Fig. 2). Plasma MMA was inversely associated with m-MMSE and KOLT scores in depressed participants in linear

TABLE 4. Significant Associations in Multiple Linear Regression Models of the Interaction Between Vitamin B_{12} Markers and ApoE ε4 Status or HADS-D Score on the Six Cognitive Tests

	Coefficient	*p*
m-MMSE		
Vitamin B_{12} × ApoE ε4	0.861	.013
Vitamin B_{12} × HADS-D	0.701	.038
HoloTC × HADS-D	0.571	.019
MMA × HADS-D	−0.428	<.001
KOLT		
Vitamin B_{12} × HADS-D	0.952	.004
HoloTC × HADS-D	0.561	.018
MMA × HADS-D	−0.368	<.001
m-DST		
Vitamin B_{12} × ApoE ε4	0.918	.006
TC saturation × HADS-D	1.233	.29
MMA × HADS-D	−0.271	.006
COWAT		
Vitamin B_{12} × HADS-D	0.74	.025
HoloTC × HADS-D	0.546	.019
TMT-A		
MMA × HADS-D	0.357	<.001
m-BD		
MMA × HADS-D	−0.303	.005

ApoE = apolipoprotein E;HADS-D = Hospital Anxiety and Depression Scale, depression subscale; m-MMSE = modified version of the Mini-Mental State Examination; holoTC = holotranscobalamin; MMA = methylmalonic acid; KOLT = Kendrick Object Learning Test; m-DST = modified version of the Digit Symbol Test; TC = transcobalamin; COWAT = abridged version (S-task) of the Controlled Oral Word Association Test; TMT-A = part A of the Trail Making Test; m-BD = modified version of Block Design.

Standardized regression coefficients are presented.

Log-transformed data of the plasma vitamin B_{12} status variables were used in all analyses.

Variables in the model are as follows: sex, ApoE ε4 status, education, diabetes, hypertension, cardiovascular disease, HADS-D score, plasma creatinine, vitamin B_{12} markers × ApoE ε4 status, and vitamin B_{12} markers × HADS-D score.

regression models (Table 5, Fig. 3). A 10% increase in MMA levels was associated with a 0.3- and 1.6-unit decrease in m-MMSE and KOLT scores, respectively (Table 5).

High plasma tHcy was associated with deficit in episodic memory, although when stratified by sex, a significant inverse association was found only among men (p = .001 for men, p = .129 for women). A significant, although weak association with episodic memory scores was observed for the holoTC/B_{12} ratio (partial r = 0.07, p = .015) and MMA (partial r = −0.05, p = .038) in linear regression models (Table 3). There was a significant interaction between depression scores and vitamin B_{12}, holoTC, and MMA on KOLT scores (Table 4). In depressed participants, there was a stronger inverse association between high plasma MMA and KOLT scores (Table 5, Fig. 3), and the associations with low holoTC and TC saturation almost reached significance (p = .059 for holoTC, p = .056 for TC saturation). For m-DST test scores, a weak inverse association with vitamin B_{12} was observed (Table 3), whereas a significant interaction on m-DST scores was observed between vitamin B_{12} and ApoE ε4 (Table 4). In depressed participants, COWAT scores were positively and more strongly associated with low holoTC and TC saturation (Table 5, Fig. 3). High MMA was associated with poor scores on TMT-A in participants with the ApoE ε4 allele, but not in those without ApoE ε4 (Table 5, Fig. 2). High tHcy presented a positive association with TMT-A scores in linear regression models, although when stratified by sex, high plasma tHcy was associated with cognitive deficit on TMT-A only in men (p = .047 for men, p = .186 for women). The holoTC/B_{12} ratio had a significant positive association with m-BD test scores only in those positive for ApoE ε4 (Table 5).

DISCUSSION

In this large population-based sample of Norwegian elderly, the most significant finding is that the association of vitamin B_{12} status with cognitive test performance is stronger in the presence of the ApoE ε4 allele or in the presence of depression. The relatively weak independent association may be related to the good vitamin B_{12} status in this elderly population. As previously reported, the low prevalence of vitamin B_{12} deficiency in these community-dwelling elderly was related to high vitamin B_{12} intake, which may be related to the high dietary intake of milk and fish among our participants (51).

The prevalence of vitamin B_{12} deficiency in this population was lower than that frequently documented among the elderly (6). Low vitamin B_{12} status may affect up to 43% of the elderly population, as demonstrated by the use of various markers of vitamin B_{12} status: low or low-normal vitamin B_{12} levels with or without high MMA and tHcy, and low holoTC concentrations (6,7,52–54). In our study, only 5.9% of the participants were considered deficient in vitamin B_{12} (plasma vitamin B_{12} <200 pM), whereas 5.1% had high plasma MMA (>0.37 μM).

Our findings are in agreement with the results of recent studies suggesting an interaction of vitamin B_{12} status and ApoE ε4 genotype on cognitive function (2,3). Individuals with the ApoE ε4 allele have a significantly higher risk for cognitive decline (55) and perform significantly worse on measures of episodic memory, executive functioning, and overall global cognitive ability (2,3,39). In the current study, plasma vitamin B_{12} was positively related to global cognition (m-MMSE), but this association was observed only in those positive for ApoE ε4.

In our study, plasma holoTC and the holoTC/B_{12} ratio were positively related to global cognition scores. In a recent study (7), holoTC was associated with Mini-Mental State Examination scores, whereas in the Oxford Healthy Aging Project, greater cognitive decline over 10 years was associated with lower holoTC concentrations at baseline (56). Thus, low levels of holoTC frequently occur in Alzheimer's disease (57). However, another smaller study found no significant correlations between holoTC and cognitive scores (53). We observed that among depressed participants, COWAT scores were positively associated with holoTC and TC saturation. This is consistent

TABLE 5. Significant Associations in Multiple Linear Regression Models for Cognitive Test Scores Stratified by ApoE ε4 Status and Depression Score

	ApoE ε4–Negative				ApoE ε4–Positive			
	R^a	Coefficient	Partial *r*	*p*	R^a	Coefficient	Partial *r*	P^a
m-MMSE								
Vitamin B_{12}	0.052	−0.105	−0.03	.369	0.056	0.504	0.11	.015
MMA	0.053	−0.190	−0.04	.137	0.053	−0.437	−0.10	.036
TMT-A								
MMA	0.052	1.401	0.01	.798	0.090	20.651	0.11	.014
m-BD								
HoloTC/B_{12} ratio	0.023	−0.265	−0.02	.522	0.070	1.671	0.11	.021
	Depression Score ≤7				Depression Score >7			
	R^a	Coefficient	Partial *r*	*p*	R^a	Coefficient	Partial *r*	P^b
m-MMSE								
MMA	0.043	−0.111	−0.03	.282	0.185	−2.725	−0.31	<.001
KOLT								
MMA	0.072	−1.293	−0.03	.268	0.198	−16.351	−0.29	.001
COWAT								
HoloTC	0.107	−0.193	−0.01	.779	0.149	5.668	0.20	.038
TC saturation	0.106	0.067	0.01	.925	0.148	5.066	0.20	.038

ApoE = apolipoprotein E; m-MMSE = modified version of the Mini-Mental State Examination; MMA = methylmalonic acid; TMT-A = part A of the Trail Making Test; m-BD = modified version of Block Design; holoTC = holotranscobalamin; KOLT = Kendrick Object Learning Test; COWAT = abridged version (S-task) of the Controlled Oral Word Association Test.

Unstandardized regression coefficients are presented.

Log-transformed data of the independent variables were used in all analyses.

[a] Adjusted for sex, education, diabetes, hypertension, cardiovascular disease, plasma creatinine, and Hospital Anxiety and Depression Scale, depression subscale score.

[b] Adjusted for sex, ApoE ε4 status, education, diabetes, hypertension, cardiovascular disease, and plasma creatinine.

with a recent study in which the significant association between the holoTC/B_{12} ratio and cognitive function was confined to those participants with depressive symptoms (4).

The results of our study are consistent with the findings of previous cross-sectional studies reporting significant associations between lower performance in global cognition test

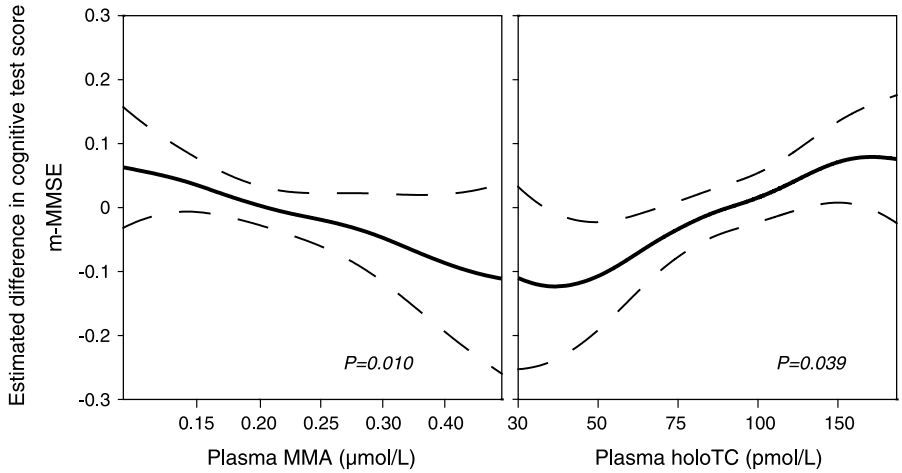

Figure 1. Associations between different cognitive test scores and plasma vitamin B_{12} status, obtained by additive Gaussian generalized regression models. Multiple adjustments included sex, ApoE ε4 status, education, diabetes, hypertension, cardiovascular disease, HADS-D score, and plasma creatinine. Solid lines represent estimated dose-response curves, and dashed lines represent 95% confidence intervals. *p* values are derived from corresponding multiple linear regression analyses. The lowest and highest 2.5 percentiles of plasma variables are not presented. ApoE, apolipoprotein E; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; m-MMSE, modified version of the Mini-Mental State Examination; MMA, methylmalonic acid; holoTC, holotranscobalamin.

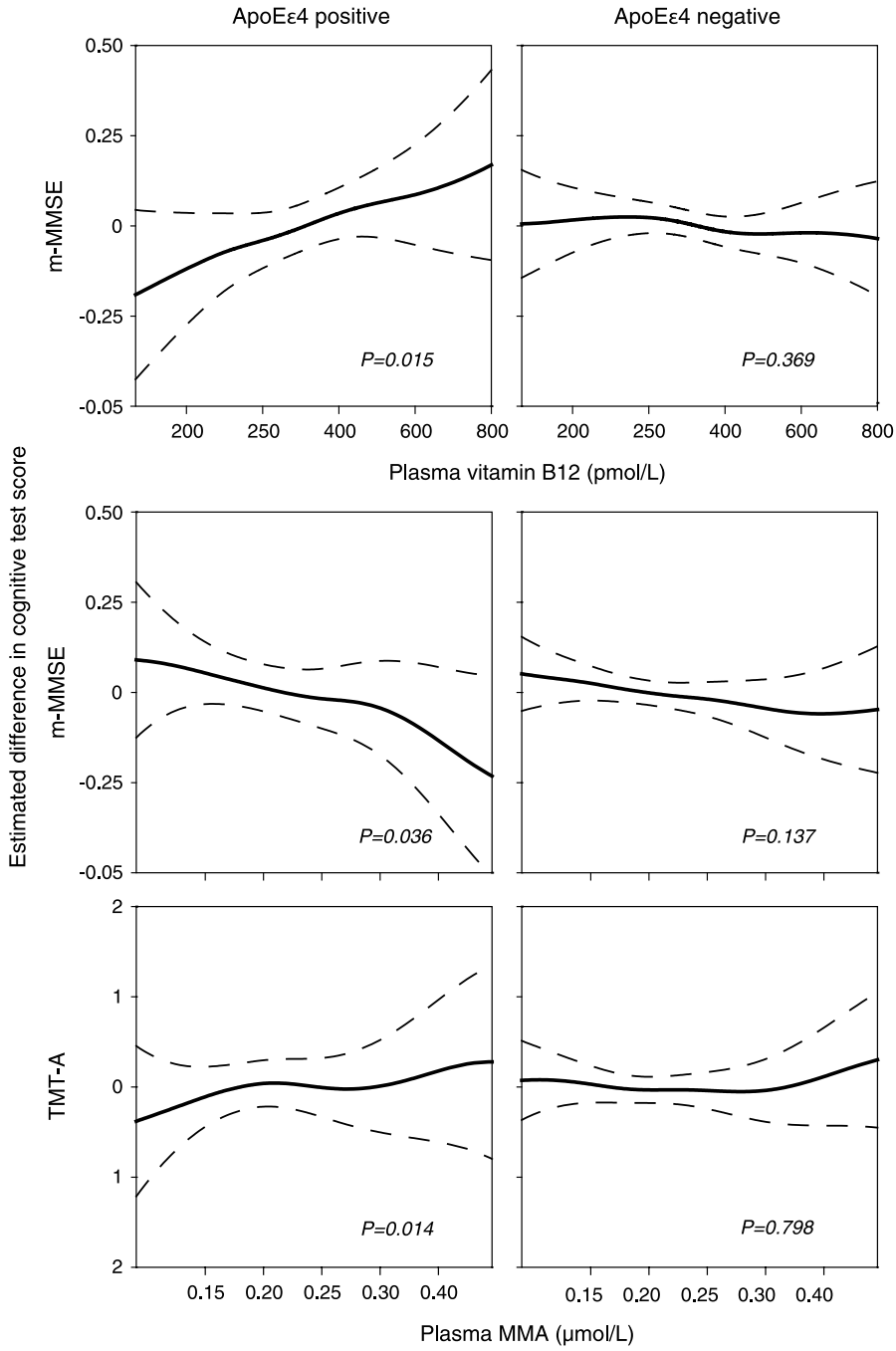

Figure 2. Associations between different cognitive test scores and plasma vitamin B_{12} status stratified by ApoE ε4 status, obtained by additive Gaussian generalized regression models. Multiple adjustments included sex, education, diabetes, hypertension, cardiovascular disease, HADS-D score, and plasma creatinine. Solid lines represent estimated dose-response curves, and dashed lines represent 95% confidence intervals. *p* values are derived from corresponding multiple linear regression analyses. The lowest and highest 2.5 percentiles of plasma variables are not presented. ApoE, apolipoprotein E; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; m-MMSE, modified version of the Mini-Mental State Examination; TMT-A, part A of the Trail Making Test; MMA, methylmalonic acid.

scores and high levels of MMA (7,53). Other studies report associations with high levels of MMA and lower performance in various cognitive domains, such as spatial skills (58), information processing speed, memory, verbal fluency, and nonverbal reasoning (59). Two recent prospective studies have reported that greater cognitive decline was associated with higher MMA concentrations (54,56). However, not all studies have confirmed a correlation between MMA and impaired cognitive function (60,61), and there are conflicting data as to whether MMA concentrations are elevated in patients with dementia (57,62).

It is noteworthy that, in the present study, the inverse association between levels of MMA and global cognition was observed only in those positive for ApoE ε4 and in participants with depression. The interactions between the ApoE ε4 allele, depression, and MMA on cognition are not well documented.

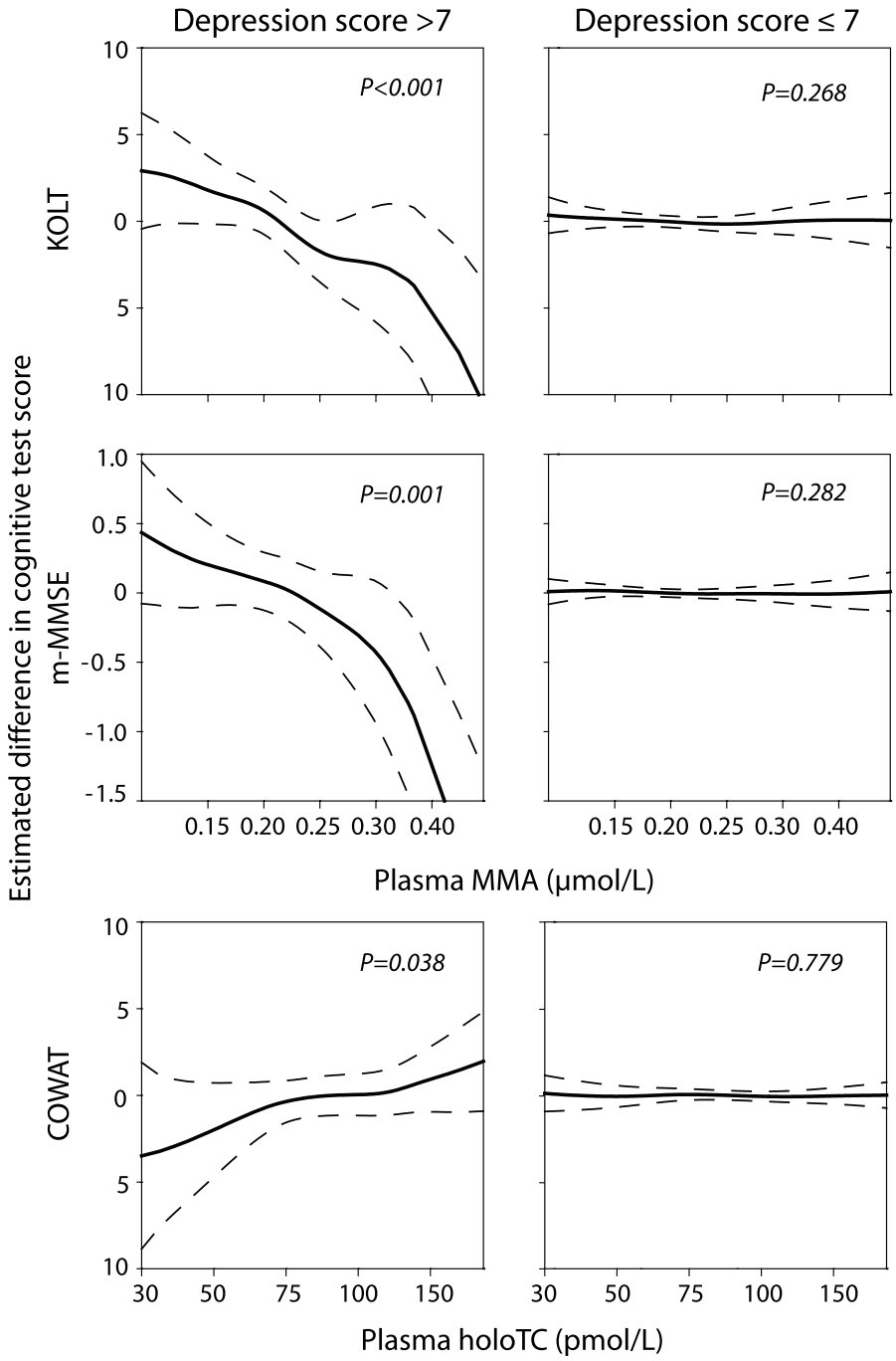

Figure 3. Associations between different cognitive test scores and plasma vitamin B_{12} status stratified by depression score, obtained by additive Gaussian generalized regression models. Multiple adjustments included sex, ApoE ε4 status, years of education, diabetes, hypertension, cardiovascular disease, and plasma creatinine. Solid lines represent estimated dose-response curves, and dashed lines represent 95% confidence intervals. *p* values are derived from corresponding multiple linear regression analyses. The lowest and highest 2.5 percentiles of plasma variables are not presented. ApoE, apolipoprotein E; KOLT, Kendrick Object Learning Test; m-MMSE, modified version of the Mini-Mental State Examination; MMA, methylmalonic acid; COWAT, abridged version (S-task) of the Controlled Oral Word Association Test.

Although limited, there is evidence that the associations between vitamin B_{12} status and cognitive function scores are stronger in patients with depression than in participants without depression (4,28,37). Decreased performance on visual memory and verbal fluency tests has been reported in depressed people with low vitamin B_{12} levels (37). Although data on depression and MMA are limited, in the American Women's Health and Ageing Study, depressed participants, especially those with severe depression, had significantly higher MMA than the mentally well participants (34).

As described in another report from the Hordaland Homocysteine Study, elevated plasma tHcy was associated with low

episodic memory performance (63). Although high plasma tHcy was associated with lower performance in episodic memory in the current study, there was no evidence of effect modification on this association by low levels of vitamin B_{12}. This is probably attributable to the low number of participants with high plasma tHcy and low vitamin B_{12}. It has also been reported that the association of tHcy with cognition is modified by the presence of the ApoE ε4 allele (64). However, in our present study, no interaction was observed between plasma tHcy and ApoE status.

This study overcame several limitations of previous studies, such as the use of a single marker of vitamin B_{12} status, so that more subtle associations were detected. Furthermore, the use of various cognitive tests assessing different domains of cognitive function is an advantage. Other strengths include the size of the cohort and its population-based setting. However, several limitations should be taken into considerations. The study's cross-sectional design does not allow interpretation of causality and cannot demonstrate whether the observed association with vitamin B_{12} status precedes or results from the cognitive impairment or depression. Moreover, multiple significance testing was conducted, and it is possible that spurious significant associations could be observed.

Another possible drawback is that the impaired cognition or depression itself may have caused the low vitamin B_{12} status by an alteration of the diet and its quality through decreased food intake. This is unlikely in this sample because participants were not seriously impaired. However, it cannot be ruled out that cognitive impairment causes both depressive symptoms and low vitamin B_{12} status via unrecognized pathophysiological mechanisms or behavioral modifications affecting dietary intake of vitamin B_{12}. Finally, not all participants completed the entire neuropsychological test battery owing to participant compliance. Results for tests with relatively small sample sizes could be affected by selection bias and should be interpreted cautiously.

The presence of additional factors (ApoE ε4 allele and depression) that contribute to cognitive impairment strengthened the associations between low vitamin B_{12} status and cognition. Although the biological mechanisms by which ApoE ε4 or depression modulates the effects of low vitamin B_{12} on cognitive function are unknown, we hypothesize that patients with the ApoE ε4 allele or patients exhibiting depressive symptoms may be those most likely to benefit from vitamin B_{12} supplementation in an elderly population. Long-term trials in participants with low vitamin B_{12} status are required to assess the relevance of vitamin B_{12} supplementation to the prevention of cognitive decline in older people, and we suggest that such trials be stratified into those with and without the ApoE ε4 allele or into those with and without depression.

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