Increases in Homocysteine Are Related to Worsening of Stroop Scores in Healthy Elderly Persons: A Prospective Follow-up Study

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Background. Elevated blood levels of homocysteine have been associated with cerebrovascular disease and cognitive impairment. The authors’ objective was to determine the relationship between cognitive changes and variations in tHcy levels over time in healthy elderly volunteers.

Methods. This prospective cohort study was conducted in healthy community-dwelling older adults without cerebrovascular disease at baseline and followed them for 2.3 years. Cobalamin, red blood cell folate, total serum homocysteine (tHcy), and creatinine levels were measured and recorded. Cognitive measures included the Mini Mental State Examination, California Verbal Learning Test, Mattis Dementia Rating Scale, and Stroop Neuropsychological Inventory.

Results. At baseline, participants with elevated tHcy levels had lower Stroop scores (72.7 vs 85.35, p < .05) than did participants with normal tHcy levels. The tHcy levels correlated significantly with Stroop scores at baseline and follow-up. At follow-up, tHcy levels had increased in 104 participants (group I) and decreased in 76 participants (group II). Compared to baseline, tHcy levels increased significantly at follow-up (p < .05 and p < .001, respectively). Participants in group I had significantly lower Stroop scores in multivariate analyses at follow-up than at baseline. The scores of participants in group II at follow-up were not significantly different than their scores at baseline. The rate of change of tHcy levels and the rate of change of the Stroop scores were significantly correlated (r = −0.264, p < .001) after multivariate analysis. Stroop scores decreased by 22% at follow-up in participants whose tHcy levels increased by 40% from baseline to follow-up.

Conclusion. Elevated tHcy levels and increases in tHcy during a short period of time are associated with decreased Stroop scores in otherwise cognitively normal elderly volunteers.

The relation between elevated total serum homocysteine (tHcy) levels and cognitive function in elderly persons has been investigated in recent years, but the studies have yielded various results. In a 5-year follow-up study, McCaddon and colleagues (1) first reported an association between baseline tHcy levels and cognitive scores at follow-up in a small group of elderly persons with normal cognitive function at baseline. A previous study (2) using the Mini-Mental State Examination (MMSE) as the only measure of cognitive function found no association between baseline tHcy and decreases in the MMSE score in a follow-up 2.7 years later. In cross-sectional studies, no association between tHcy scores and cognitive function was found in a small population study (3). However, in larger populations, investigators noted significant associations between poor visuospatial performance and high tHcy levels (4), between low delayed recall of story ideas and tHcy levels (5), and between MMSE scores and high tHcy levels (6). Duthie and colleagues (7) also found that tHcy levels were associated with cognitive changes in older persons and accounted for 7% to 8% of the variance in cognitive performance.

Elevated tHcy levels have also been found to be an independent risk factor for the development of Alzheimer’s disease 8 years after baseline, and that the risk increased with higher levels of tHcy at baseline. Similarly, an association between elevated tHcy and dementia has been described in various populations (9–13). In a recent review article, Lökk (14) referred to tHcy as the most sensitive marker of cobalamin/folic acid metabolic function and the factor that correlates most strongly with parameters of cognition.

It is unclear at this point which are the early cognitive changes associated with elevated tHcy, what are the effects of increases of tHcy levels over time on cognitive function of otherwise healthy older adults, or whether reduction of tHcy levels is followed by changes in cognitive function. To address these questions, we conducted a prospective study in a large cohort of cognitively normal adults at baseline.

Methods

Participants

One hundred eighty participants tested at baseline were retested after an average of 2.3 years between 2001 and 2002. This cohort was part (64%) of the original baseline cohort that included 281 community-dwelling volunteers, aged 65 years and older. Baseline exclusion criteria consisted of participant use of oral cobalamin (>37.5 μg/day) or any injected dose; history of ileal or gastric surgery; renal failure
(creatinine level >130 µmol/L); neurologic disease (i.e.,
stroke, severe head trauma, Parkinson’s disease); depression,
(based on a Geriatric Depression Rating Scale score >6 of
15); an MMSE score less than 24 of 30; hospitalization
during the 3 months before testing; and any acute medical
condition. Participants were recruited at community seniors’
meetings and all gave written informed consent. The
university and the hospital ethics committees approved the
study. In Canada, fortification of wheat products with folic
acid was in effect after the study began.

Laboratory Investigations

Serum cobalamin, red blood cell (RBC) folate, and
creatinine levels were determined by standard procedures.
The tHcy determinations were made by Metabolite Labs
(Denver, CO) using capillary gas chromatography–mass
spectrometry and high-performance liquid chromatography
(15). Serum samples were obtained within 30 minutes of
blood collection and maintained at ~70°. Normal values are
cobalamin, 165 to 740 pmol/L; RBC folate, 200 to 1300
nmol/l; and tHcy, 5.1 to 13.9 nmol/l.

Data were collected systematically, both at baseline and at
follow-up, on participant demographic factors, medical his-
tory, medications, and diet. Hypertension was defined in
accordance with the World Health Organization criteria as
a systolic blood pressure of 160 mmHg or more, a diastolic
blood pressure of 95 mmHg or more, or the use of anti-
hypertensive medication. Diabetes mellitus was defined
according to the criteria of the American Diabetes Association
or by the participant’s use of diabetes mellitus medications.

Psychometric Measures

Cognitive tests administered included the Stroop Neuro-
psychological Screening Test (16), the Mattis Dementia
Rating Scale (DRS) (17), and the California Verbal Learning
Test (CVLT) (18). The Stroop is a test of executive function
measuring attention and concentration in the face of
interference and cognitive flexibility. In this test, the partici-
 pant is asked to read a list of color names, each printed in
a noncorresponding ink color. Then the participant is asked
to name the colors of the ink, not the written word, from
a second, different list. Executive functions are defined as
high-level cognitive functions involved in the control and
direction of lower-level functions (19). The Mattis DRS is
a screening test for dementia and includes subsets for
attention, initiation and perseveration, construction, concep-
tualization, and memory. The CVLT is a verbal learning test
that assesses verbal memory (recall, recognition, cuing ef-
effects, types of errors, and learning characteristics) and the
effect of interference on recall and recognition. The CVLT
compiles 27 outcome variables into 5 main categories (recall
measures, learning characteristics, recall errors, recognition
measures, and contrast measures). An MMSE was also
administered in the follow-up visit and the scores were
compared with those recorded at baseline.

Statistical Analyses

Differences between cognitive scores at baseline and
follow-up were measured using the paired Student’s t test.
An unpaired t test was used to compare the differences
between participants with elevated and participants with
normal tHcy levels, and differences at baseline between
participants who were followed and those who were not.
Pearson’s coefficients were used to assess the relation be-
tween cognitive scores and tHcy at baseline and follow-up.

For the follow-up analysis, we separated the participants
into two groups: those who had a significant increase in
tHcy levels from baseline to follow-up (group I), and those
who had a significant decrease in tHcy levels (group II). We
calculated the rate of change for Stroop scores and tHcy
levels between the baseline and follow-up measurements for
each participant as the value at follow-up minus the value at
baseline divided by the value at baseline. In group I (those
who experienced a tHcy increase), we separated the partici-
ants into five percentiles according to the percentage of
change of tHcy level (<10%, 10.1%–20%, 20.1%–30%,
30.1%–40%, and >40%). We compared the mean changes
of the Stroop score in these five subgroups using analysis of
variance and post hoc tests.

We performed linear regression analyses to identify inde-
pendent predictors of the rate of change in Stroop scores. We
included in the regression model as independent variables
age, education, sex, cobalamin level, RBC folate level, tHcy
level, and diagnoses of diabetes mellitus and hypertension.
All tests were two sided and a probability value less than .05
was considered to be statistically significant. We used SPSS
software (version 11; Chicago, IL) for all analyses.

RESULTS

We found no differences in demographic distribution,
clinical features, cognitive test scores, or laboratory results
at baseline between the participants who were followed and
those who did not return for the follow-up visit. Therefore,
we based all calculations on the 180 participants from whom
we obtained data at baseline and follow-up. Sixteen (8.9%)
participants at baseline and 12 (6.7%) participants at follow-
up had elevated tHcy levels (>13.9 nmol/l). This relatively
low percentage of participants with high tHcy levels is
probably the result of the folic acid fortification program.
None of the participants had levels greater than 50 nmol/l.
Among the 16 participants with high tHcy levels at baseline,
9 had normal tHcy levels at follow-up. Participants with
elevated tHcy levels at baseline had significantly lower
Stroop scores (72.7 ± 21.97 vs 85.35 ± 17.51; p < .05) but
similar CVLT, DRS, and MMSE scores compared with
participants with normal tHcy levels. Differences in Stroop
scores between participants with elevated tHcy levels and
those with normal tHcy levels at follow-up were not statis-
tically significant.

Univariate analyses showed a significant correlation
between tHcy levels and Stroop scores at baseline (r =
-.146, p < .05) and at follow-up (r = -.126, p < .05) but no
significant correlation between tHcy levels and the other
cognitive scores (MMSE, DRS, CVLT) at baseline or at
follow-up.

When we compared the psychometric test scores at
baseline with scores obtained at follow-up among all the
participants, we found significant decreases in the Stroop
(p = .001) and CVLT scores (p < .001) (data not shown).
The mean rate of change for the Stroop score from baseline to

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follow-up was −3.5%, and the mean rate of change for total recall trials 1 to 5 of the CVLT was −3.3%. The rate of change of the Stroop score was significantly correlated with the rate of change of tHcy levels \( (r = -0.223, p = .003) \), but we found no correlation between the rate of change of tHcy and the rate of change of the CVLT scores.

From baseline to follow-up, 104 participants had a significant increase in their tHcy levels (group I) (8.87 vs 10.4, \( p < .05 \)), and 76 participants had a significant decrease of tHcy levels (group II) (12.0 vs 9.3, \( p < .001 \)). Table 1 shows the characteristics of the two groups. We found no differences between the 2 groups in relation to age, years of education, and time interval between baseline and follow-up testing. However, cobalamin, creatinine, and RBC folate levels and the prevalence of hypertension all differed between the two groups. Comparison of baseline scores of participants in groups I and II showed that the CVLT and DRS total scores were similar between the two groups, but the mean Stroop score was higher in group I than in group II (86.7 vs 81.0, \( p < .05 \)).

Table 2 shows the changes in cognitive scores in the two groups. Participants in group I had significantly lower scores for the Stroop test at follow-up (\( p < .005 \)) compared with baseline. They also showed worsening of verbal memory as assessed by a significant decrease in the CVLT, including total recall list A trials 1 to 5, trial 1, trial 5, list B, short-delay cued recall, long-delay free recall, errors (free, cued, and total), recognition, discriminability, false positives, response bias, contrast measures list B to list A, and recognition compared with long-delay free recall. However, in group II, we found few significant changes in CVLT and no significant changes in Stroop scores at follow-up.

We noted significant differences between groups I and II in the rate of change of Stroop scores (−5.25% vs −0.5%, \( p < .05 \)) and rate of change of levels of tHcy (18.5% vs −17.5%, \( p < .001 \)), respectively. Group I showed a significant correlation between the rate of change of tHcy and the rate of change in Stroop score \( (r = -0.272, p = .007) \), but we found no correlation between the two parameters in group II. The rate of change of CVLT total recall trials 1 to 5 score did not correlate with the rate of change of tHcy level in group I.

As shown in Table 3, tHcy levels increased by more than 40% from baseline to follow-up in 8.7% participants (all were <14 nmol/L and, therefore, within normal limits for our laboratory), and Stroop scores decreased by 22%. The rate of change in Stroop scores was not significant among participants whose tHcy levels increased by less than 40%.

In multivariate analyses of all participants, we included the following covariates and possible confounders that might affect the Stroop scores: age, education, time interval between the two visits, cobalamin, RBC folate levels, diabetes, and hypertension. The results showed that the rate of change in tHcy levels was significantly associated with the rate of change in Stroop scores \( (p < .001) \) (Table 4).

**DISCUSSION**

These results indicate an early, significant association between changes in tHcy levels and a measure of executive cognitive function. tHcy levels were significantly correlated with the rate of change of the Stroop score. However, we found no correlation between the rate of change of tHcy and the rate of change of the CVLT scores. These results indicate an early, significant association between changes in tHcy levels and a measure of executive cognitive function. tHcy levels were significantly correlated with the rate of change of the Stroop score. However, we found no correlation between the rate of change of tHcy and the rate of change of the CVLT scores.

**Table 1. Characteristics of the Study Population at Baseline and Follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 104)</th>
<th>Group II (n = 76)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing, y</td>
<td>72.5 ± 4.8</td>
<td>73.4 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Women, %</td>
<td>71.2</td>
<td>73.7</td>
<td>NS</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.2 ± 3.1</td>
<td>13.6 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE, /30</td>
<td>28.4 ± 1.6</td>
<td>28.5 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Interval between visits, y</td>
<td>2.3 ± 0.7</td>
<td>2.2 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total tHcy at visit 1, μM</td>
<td>8.9 ± 2.4</td>
<td>12.1 ± 6.2</td>
<td>.001</td>
</tr>
<tr>
<td>Total tHcy at visit 2, μM</td>
<td>10.4 ± 2.6</td>
<td>9.3 ± 2.3</td>
<td>.004</td>
</tr>
<tr>
<td>High tHcy at visit 1, %</td>
<td>4.8</td>
<td>13.2</td>
<td>.001</td>
</tr>
<tr>
<td>High tHcy at visit 2, %</td>
<td>9.6</td>
<td>2.6</td>
<td>.001</td>
</tr>
<tr>
<td>Chl at visit 1, μmol/L</td>
<td>359.9 ± 288</td>
<td>254.5 ± 115</td>
<td>.001</td>
</tr>
<tr>
<td>Chl at visit 2, μmol/L</td>
<td>409 ± 227</td>
<td>379.4 ± 202</td>
<td>NS</td>
</tr>
<tr>
<td>RBC folate at visit 1, mmol/L</td>
<td>988.2 ± 432.5</td>
<td>790.7 ± 401.2</td>
<td>.002</td>
</tr>
<tr>
<td>RBC folate at visit 2, mmol/L</td>
<td>1602.4 ± 550.0</td>
<td>1371.1 ± 512.0</td>
<td>.005</td>
</tr>
<tr>
<td>Creatinine at visit 1, μmol/L</td>
<td>71.1 ± 14.6</td>
<td>76.5 ± 14.9</td>
<td>.05</td>
</tr>
<tr>
<td>Creatinine at visit 2, μmol/L</td>
<td>76.1 ± 16.7</td>
<td>76.5 ± 14.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>10.6</td>
<td>9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>28</td>
<td>48</td>
<td>.015</td>
</tr>
</tbody>
</table>

NS = not significant; Group I = subjects with a significant increase of tHcy at follow-up compared to baseline; Group II = subjects with a significant decrease of tHcy at follow-up compared to baseline.

We found no association between increases in tHcy levels and global cognitive function, measured by DRS or MMSE scores, at the 2.3 years of follow-up in our population, whereas Seshadri and colleagues (8) found a significant decrease in the MMSE scores in participants with elevated...
Table 2. Cognitive Scores at Baseline and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 104)</th>
<th>Group II (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.5 ± 1.5</td>
<td>28.3 ± 1.2</td>
</tr>
<tr>
<td>Stroop</td>
<td>87.3 ± 18.1</td>
<td>82.7 ± 21.0**</td>
</tr>
<tr>
<td>DRS Total</td>
<td>139.5 ± 4.0</td>
<td>139.4 ± 4.5</td>
</tr>
<tr>
<td>CVLT: Recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List A 1–5</td>
<td>51.3 ± 10.0</td>
<td>48.4 ± 11.1**</td>
</tr>
<tr>
<td>Tr 1</td>
<td>7.4 ± 2.3</td>
<td>6.7 ± 2.2**</td>
</tr>
<tr>
<td>Tr 5</td>
<td>11.7 ± 2.2</td>
<td>11.2 ± 2.6*</td>
</tr>
<tr>
<td>List B</td>
<td>6.8 ± 2.3</td>
<td>5.8 ± 2.3**</td>
</tr>
<tr>
<td>SD FR</td>
<td>9.3 ± 3.1</td>
<td>9.0 ± 3.4</td>
</tr>
<tr>
<td>SD CR</td>
<td>10.9 ± 2.3</td>
<td>10.4 ± 2.8*</td>
</tr>
<tr>
<td>LD FR</td>
<td>10.2 ± 2.9</td>
<td>9.7 ± 3.4*</td>
</tr>
<tr>
<td>LD CR</td>
<td>11.0 ± 2.7</td>
<td>10.6 ± 2.9</td>
</tr>
<tr>
<td>Learning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic Cl&amp; R</td>
<td>2.13 ± .90</td>
<td>2.13 ± .91</td>
</tr>
<tr>
<td>Serial Cl R</td>
<td>2.2 ± 1.8</td>
<td>2.1 ± 1.6</td>
</tr>
<tr>
<td>% correct primacy</td>
<td>29.3 ± 5.7</td>
<td>29.2 ± 6.66</td>
</tr>
<tr>
<td>% correct middle</td>
<td>43.5 ± 7.7</td>
<td>42.1 ± 7.8</td>
</tr>
<tr>
<td>% correct recency</td>
<td>27.1 ± 5.7</td>
<td>28.6 ± 6.6*</td>
</tr>
<tr>
<td>Slope (words/trial)</td>
<td>.99 ± .47</td>
<td>1.04 ± .56</td>
</tr>
<tr>
<td>% recall consist</td>
<td>81.1 ± 9.2</td>
<td>78.9 ± 11.7*</td>
</tr>
<tr>
<td>Errors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverations</td>
<td>4.2 ± 3.5</td>
<td>3.8 ± 3.8</td>
</tr>
<tr>
<td>FR intrusions</td>
<td>2.1 ± 2.5</td>
<td>2.7 ± 3.7*</td>
</tr>
<tr>
<td>CR intrusions</td>
<td>1.9 ± 2.2</td>
<td>2.4 ± 2.7*</td>
</tr>
<tr>
<td>Total intrusions</td>
<td>4.0 ± 4.3</td>
<td>5.2 ± 5.9*</td>
</tr>
<tr>
<td>Recognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hits</td>
<td>14.5 ± 1.5</td>
<td>14.8 ± 1.4*</td>
</tr>
<tr>
<td>Discriminability</td>
<td>93.8 ± 5.3</td>
<td>92.8 ± 6.3*</td>
</tr>
<tr>
<td>False positives</td>
<td>1.3 ± 1.7</td>
<td>2.0 ± 2.4**</td>
</tr>
<tr>
<td>Response bias</td>
<td>-.051 ± .334</td>
<td>.081 ± .358**</td>
</tr>
<tr>
<td>Contrasts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List B - A Tr1</td>
<td>-.20 ± 41.4</td>
<td>-.12 ± 28.7*</td>
</tr>
<tr>
<td>SD FR - List A Tr5</td>
<td>-21.5 ± 20.8</td>
<td>-20.6 ± 21.6</td>
</tr>
<tr>
<td>LD FR - SD FR</td>
<td>14.8 ± 32.6</td>
<td>12.6 ± 35.3</td>
</tr>
<tr>
<td>Recognition</td>
<td>51.8 ± 48.5</td>
<td>77.3 ± 77.6**</td>
</tr>
</tbody>
</table>

MMSE = Mini Mental State Examination; DRS = Dementia Rating Scale Total score; CVLT = California Verbal Learning Test; SD = short delay; FR = free recall; CD = cued recall; LD = long delay; Cl& R = cluster ratio; Tr = trial; consist = consistency. Group I = subjects with a significant increase of tHcy at follow-up compared to baseline; group II = subjects with a significant decrease of tHcy at follow-up compared to baseline. Significant differences between visit 1 and visit 2 *p < .05, **p < .005.

tHcy at a follow-up of 8 years (8), and den Heijer and colleagues (20) found an association between tHcy and cortical and hippocampal atrophy. In univariate analyses, we also found that verbal memory function measured by CVLT scores was significantly lower in participants whose tHcy levels had increased at follow-up, compared with participants whose tHcy levels had decreased; however, this relation was not significant after adjustment for confounding variables. McCaddon and colleagues (1) have described a significant memory decline (primarily visuospatial) in persons with elevated tHcy at a follow-up interval of 5 years. We postulate that detection of significant decreases in

Table 3. Mean Rates of Change in Stroop Scores According to Rate of Changes in tHcy Among Subjects in Group I (n = 104)*

<table>
<thead>
<tr>
<th>Rates of changes in tHcy</th>
<th>Numbers of subjects N (%)</th>
<th>Rates of changes in Stroop</th>
<th>p value for the differences between groups†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>39 (37.5)</td>
<td>-4.12%</td>
<td>NS</td>
</tr>
<tr>
<td>10–20%</td>
<td>27 (26)</td>
<td>-2.11%</td>
<td>NS</td>
</tr>
<tr>
<td>20.1–30%</td>
<td>17 (16.3)</td>
<td>-2.50%</td>
<td>NS</td>
</tr>
<tr>
<td>30.1–40%</td>
<td>12 (11.5)</td>
<td>-6.20%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>9 (8.7)</td>
<td>-22.3%</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

† Comparing to the other groups. *tHcy = homocysteine; NS = not significant.

Table 4. Linear Regression Analysis With Rate of Change in Stroop Scores as the Dependent Variable for all Subjects

<table>
<thead>
<tr>
<th>Independent predictors</th>
<th>Beta coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>-0.188</td>
<td>.017</td>
</tr>
<tr>
<td>Education, y</td>
<td>-0.151</td>
<td>.053</td>
</tr>
<tr>
<td>Interval between visits, y</td>
<td>0.024</td>
<td>.765</td>
</tr>
<tr>
<td>RBC folate, mmol/L*</td>
<td>-0.001</td>
<td>.991</td>
</tr>
<tr>
<td>tHcy (rate of change)</td>
<td>-0.264</td>
<td>.001</td>
</tr>
</tbody>
</table>

* RBC = red blood cell; tHcy = homocysteine.
executive function scores resulting from incremental increases in tHcy levels might appear earlier than declines in verbal memory or global cognitive measures. Alternatively, the association we found in our population between increases in tHcy and decreases in Stroop scores might explain, in part, the proposed decrease in the stability of executive function seen in elderly persons (21) regardless of possible future cognitive changes.

Among the multiple studies that addressed the issue of prediction of future cognitive impairment by use of various cognitive tests in nondemented populations, few have investigated executive function. Chen and colleagues (22) found that executive dysfunction (measured by the Trail Making Test, Part B) could be a subtle manifestation of incipient Alzheimer’s disease, along with memory dysfunction. The Stroop test is a measure of attention and concentration in the face of interference, a test of executive function such as use of strategy and response flexibility (focused attention). Continued follow-up of our population might clarify whether the observed decrease in Stroop scores represents a preclinical phase of further cognitive impairment or whether it is solely associated with what might be classified as “normal brain aging” without evolving into a pathologic state.

As shown in Table 1, both cobalamin and RBC folate levels increased from baseline to follow-up in all participants. We cannot explain why some persons experience increases in tHcy while others do not, but this observation might present practical questions with regard to treatment aimed at decreasing the levels of tHcy.

Recently, the relation between Alzheimer’s disease and tHcy has been attributed to the vascular effects of elevated tHcy (23). McCaddon and coworkers (24) postulated that cerebral oxidative stress increases the oxidation of an intermediate form of cobalamin generated in the methionine synthase pathway, impairing homocysteine metabolism.

Conclusion

Our results suggest that a significant relationship between increases in tHcy levels over time and decline in performance in a test of executive function exists independently of other factors in otherwise healthy elderly persons. We also observed a trend in verbal memory decline at a relatively short follow-up period. Furthermore, the results seem to indicate that levels of tHcy in the upper limit of the normal range might already be related to worsening of cognitive function, and that decreases in tHcy concentrations to the lower part of the normal range might be needed to avoid worsening of cognitive function.

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