ABSTRACT

Objective: To investigate whether supplementing older men with vitamins B₁₂, B₆, and folic acid improves cognitive function.

Methods: The investigators recruited 299 community-representative hypertensive men 75 years and older to a randomized, double-blind controlled clinical trial of folic acid, vitamin B₆, and B₁₂ supplementation vs placebo over 2 years. The primary outcome of interest was the change in the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog). A secondary aim of the study was to determine if supplementation with vitamins decreased the risk of cognitive impairment and dementia over 8 years.

Results: The groups were well-balanced for demographic and biochemical parameters. There was no difference in the ADAS-cog change from baseline to 24 months between the placebo (0.8, SD 4.0) and vitamins group (0.7, SD 3.4). The adjusted scores in the treatment groups did not differ over time (placebo 0.2 lower, $z = 0.71$, $p = 0.478$). There was a nonsignificant 28% decrease in the risk of cognitive impairment (odds ratio 0.72, 95% confidence interval 0.25–2.09) and dementia (hazard ratio 0.72, 95% confidence interval 0.29–1.78) over 8 years of follow-up.

Conclusions: The daily supplementation of vitamins B₁₂, B₆, and folic acid does not benefit cognitive function in older men, nor does it reduce the risk of cognitive impairment or dementia.

Classification of evidence: This study provides Class I evidence that vitamin supplementation with daily doses of 400 µg of B₁₂, 2 mg of folic acid, and 25 mg of B₆ over 2 years does not improve cognitive function in hypertensive men aged 75 and older.

GLOSSARY

AD — Alzheimer disease; ADAS-cog — cognitive subscale of the Alzheimer's Disease Assessment Scale; BDI — Beck Depression Inventory; CCA — complete case analysis; CVLT — California Verbal Learning Test; ICE — imputation by chained equations; ITT — intention-to-treat; MMSE — Mini-Mental State Examination; SF — Short Form; tHcy — total plasma homocysteine; TICS — Telephone Interview for Cognitive Status; WADLS — Western Australian Data Linkage System.

Dementia and cognitive impairment are major public health concerns in the 21st century.¹ High total plasma homocysteine (tHcy) has been associated with cognitive impairment and dementia,²,³ although it is unclear whether this link is causal. This is important because tHcy can be lowered by about 20% with oral supplementation of specific B-vitamins,⁴ marking it as a potentially modifiable risk factor.

Observational studies have consistently linked high tHcy to cognitive impairment,⁵ but the results of randomized trials have thus far failed to show any obvious benefits associated with tHcy-lowering therapy (table 1). These conflicting findings may be due to bias and confounding in observational studies, inclusion of prevalent cases of cognitive impairment in some trials, lack of power to measure small but important treatment effects, insufficient treatment duration, and recruitment of excessively healthy volunteers.
We designed this trial to test the long-term efficacy of tHcy-lowering treatment to decrease the progression of cognitive decline in a sample of older adults at risk of both high tHcy and cognitive impairment. We recruited a community-representative sample of older hypertensive men who were randomly allocated to double-blind treatment with vitamins or placebo for 2 years. We selected men because they have higher tHcy than women, as do people with hypertension compared with normotensive people. We powered the study to declare as significant a between-group difference of 2 points from baseline on the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog), which is considered a clinically significant difference associated with the use of cognitive enhancers.
Participants. We recruited a random sample of 299 men aged 75 years or older from a large population-based study of abdominal aortic aneurysm screening (Health in Men Study).\textsuperscript{2,12} Seventy-three of these men took part in a later follow-up telephone survey in 2008 and completed the Telephone Interview for Cognitive Status (TICS) questionnaire.\textsuperscript{23}

Participants were excluded if they had a Beck Depression Inventory (BDI)\textsuperscript{24} score $\geq 18$ or a Mini-Mental State Examination (MMSE)\textsuperscript{25} score $\leq 24$, deemed to have an illness likely to cause severe disability or death within 12 months (for example, metastatic cancer, Parkinson disease, or a history of stroke), were non-English speaking, lived in residential care facilities, or were already taking vitamin B supplements.

Standard protocol approvals, registration, and patient consent. The Human Research Ethics Committee of the University of Western Australia approved the study protocol. The trial was registered with the Australian Clinical Trials Registry (http://www.actr.org.au), trial number ACTRN012605000045617. Written informed consent was obtained from all participants.

Objectives. The primary aim of the trial was to ascertain whether treatment with vitamins B$_{12}$, B$_6$, and folic acid over 2 years would improve cognitive performance compared with placebo in older men (primary aim). Specifically, we hypothesized that men treated with vitamins would have better ADAS-cog scores compared with controls treated with placebo after 2 years (Class I level of evidence).

We also sought to study the longer-term impact of B-vitamin supplementation (secondary aim) by comparing performance on the TICS as well as a diagnosis of dementia registered in the Western Australian Data Linkage System (WADLS) (http://www.datalinkage-wa.org.au). We hypothesized that fewer men in the vitamin group would score 27 or less on the TICS (which indicates the presence of cognitive impairment)\textsuperscript{26} and that fewer men in the intervention group would die or be diagnosed with dementia.

Sample size. The sample size calculation was based on data from a meta-analysis of randomized trials of donepezil in Alzheimer disease (AD).\textsuperscript{26} We calculated that 104 completed subjects in each group would give the study 80% power to detect a difference of 2 points on the ADAS-cog change from baseline score between the groups. A study of 150 subjects per group would thus be adequately powered, assuming a dropout of 30% over 2 years.

Randomization. Participants were given consecutive numbers and allocated to active vs placebo arms based on computer-generated random permuted blocks. Blocks consisted of 8 subjects (4 subjects allocated to each group) so as to minimize the risk of having unbalanced entry into each arm of the study during the period of recruitment. An external and independent academic controlled the randomization procedures of the trial.

Interventions, blinding, and compliance. Vitamins and placebo were administered in the form of identical oral capsules. The active medication consisted of 400 $\mu$g B$_{12}$, 2 mg folic acid, and 25 mg B$_6$. These doses have been shown to be effective in lowering homocysteine levels.\textsuperscript{27} Participants were advised to consume 1 capsule every morning for 2 years. Men who consumed at least 75% of the study tablets during this 2-year trial were considered compliant. Compliance was determined by pill count and medication diaries. Participants and investigators were blinded to the group membership of men in the trial until the last follow-up assessment was completed. There were no breaches of protocol.

Assessment procedures. Participants were assessed at baseline and after 6, 12, 18, and 24 months from randomization. We collected information on age (in years), education (age at which left school), depressive symptoms (BDI), biochemical data, and alcohol use (standard drinks consumed per day in a typical week).

Surviving men were contacted from October to December 2008 and invited to participate in a telephone interview where the TICS was administered. Dementia and mortality data were obtained from the Western Australian Data Linkage System up until September 30, 2009. A diagnosis of dementia was recorded if the death certificate contained one of the following ICD-10 codes: F00 (dementia in AD), F01 (vascular dementia), F03 (unspecified dementia), and G30 (AD). Additionally, a dementia diagnosis was sought from records of inpatient admissions and outpatient contacts.

Assay techniques. Subjects had fasting blood samples taken between 8:30 and 11:00 AM and stored in iced lithium heparin tubes. Plasma and serum were separated from blood cells within 1 hour of blood collection. The samples were tested on the day of collection. Serum B$_{12}$ and red cell folate were measured by standard competitive assays using the Abbott Asym analyzer. Serum creatinine was measured by Jaffe kinetic reaction on a Roche 917 automated instrument. Total plasma homocysteine levels were determined by reverse phase high-performance liquid chromatography after treatment with tributylphosphine, deproteinization, and fluorogenic derivatization using the method of Araki and Sakyo.\textsuperscript{27} The coefficients of variation for all assays ranged from 3% to 7%.

Outcomes studied. The primary outcome measure of this study was the ADAS-cog.\textsuperscript{28} The ADAS-cog consists of 11 items measuring a range of cognitive functions, including memory, language, praxis, and attention. This study was primarily interested in whether there were any differences between the groups in their ADAS-cog scores at 2 years and whether the rate of change of ADAS-cog scores differed between groups over the 2 years. Secondary measures of interest included the California Verbal Learning Test (verbal memory),\textsuperscript{29} Mini-Mental State Examination (general cognitive screen), Digit Cancellation Test (attention),\textsuperscript{30} Clock Drawing Test (visuospatial skills and planning),\textsuperscript{31} TICS (general cognitive screen), changes in biochemical parameters (total plasma homocysteine, vitamin B$_{12}$, and folate), and quality of life (Short Form [SF]–36) (www.sf-36.org).

We addressed the secondary aim of the study by determining the proportion of participants who showed evidence of cognitive impairment (TICS $\leq 27$ or a recorded diagnosis of dementia in the Western Australian Data Linkage System) or who were deceased by September 2009.

Statistical analysis. Stata version 10 (StataCorp 2007) was used to manage and analyze the data. Descriptive statistics and graphs were used to investigate the distribution of the data at baseline. We used Student $t$ tests to compare differences between the groups for normally distributed data, the Mann-Whitney test for data without a normal distribution ($z$ statistic value), and $\chi^2$ tests to compare proportions between the groups. We used mixed-effects models to account for the intraperson correlation generated from the repeated measures of the same participant (complete case analysis [CCA]). Finally, we tried to assess the robustness of our results by evaluating the impact of missing values in an intention-to-treat analysis (ITT). We imputed miss-
ing data using the imputation by chained equations (ICE) method before applying a mixed-effects model. Five sets of imputed values were created to allow for the 185 missing (assumed to be randomly distributed) ADAS-cog values in total. Variables such as years of education, alcohol consumption, depressive symptoms, and age were included in the imputation equation.

Long-term data were investigated through dichotomous outcomes (i.e., diagnosis of dementia yes/no, deceased yes/no, TICS score \( \geq 27 \) or \( > 27 \)). We used logistic regression to study outcomes of the TICS and reported this in terms of odds ratios. We also used a Cox proportional hazards model to report on the mortality and dementia morbidity data, reporting these as hazard ratios.

**RESULTS**  
**Participant flow.** Figure 1 shows the flow of participants through the study. Men were randomly assigned placebo (n = 149) or vitamins (n = 150). Thirty-two (21%) men in the intervention and 26 (17%) in the placebo group withdrew consent or were lost during the trial (\( \chi^2 = 0.72, p = 0.396, df = 1 \)). Seventy-three men took part in the follow-up telephone interview: 41 (27%) in the intervention group and 32 (21%) in the placebo group (\( \chi^2 = 1.39, p = 0.238, df = 1 \)).

**Recruitment.** Participants were recruited from July 18, 2000, to February 6, 2002. The last ADAS-cog data point was collected on February 5, 2004, and the study code was broken in April of that year. Surviving participants were contacted from October 1, 2008, to December 15, 2008, and invited to complete a health questionnaire and the TICS.

**Baseline data.** Table 2 summarizes the baseline characteristics of participants. The groups were balanced for demographic, biochemical, and cognitive data, although men in the vitamin group were slightly older than placebo controls.

**Primary outcome.** There was minimal difference between the groups in both the adjusted and unadjusted primary outcome (ADAS-cog change from baseline) of interest (figure 2 and table 3) in the complete case analysis. Using mixed-effect models, we found that change from baseline scores did not differ over time according to treatment group (\( z = -0.38, p = 0.705 \)). The average unadjusted score was 0.3 points higher (SE 0.38, \( p = 0.478 \)) in the intervention group. There was no difference between the groups when adjustments were made for age, harmful alcohol use, BDI scores, and education (intervention 0.2 higher, \( z = 0.71, p = 0.478 \)).

ITT analyses showed that treatment groups did not differ over time (\( t = 0.90, p = 0.367 \)), and the average unadjusted score in the intervention group was 0.2 points higher than in the placebo group (SE 0.46, \( p = 0.602 \)). Similar results were obtained after adjustment for confounding (\( t = 0.28, p = 0.779 \)).

It has been suggested that people with higher tHcy benefit most from homocysteine-lowering treatment. We investigated this hypothesis by performing a separate subgroup analysis (CCA and ITT) for men with tHcy \( \geq 15 \) \( \mu \text{mol/L} \) at baseline. The treatment groups did not differ over time (\( z = -0.90, p = 0.369 \)). Mean adjusted ADAS-cog change score was 0.3 points lower in men taking vitamins (\( z = -0.45, p = 0.655 \)). ITT analysis produced similar results (\( t = -0.59, p = 0.554 \)).

An additional subgroup analysis looked at men who met the criteria for the diagnosis of mild cognitive impairment at baseline based on a long-delay free recall score on the California Verbal Learning Test (CVLT) of 1.5 SD below their age-appropriate normative value. The mean ADAS-cog scores at baseline in the placebo and intervention groups were 17.7 (SD 5.8) and 15.4 (SD 6.4) (\( t = 1.35, p = 0.184 \)). The groups differed by 1.2 points (SE 1.13) on the adjusted ADAS-cog when we used a mixed models approach to analyze the change from baseline, but this was not significant nor did it change when the groups were analyzed following imputation—difference of 1.1 point between groups (SE 1.19, \( p = 0.368 \)). The 2 groups did not differ over time (\( z = 0.52, p = 0.602 \)).

Finally, the correlations between changes in ADAS-cog scores from baseline to 24 months with changes in tHcy (\( r = -0.08 \)), B12 (\( r = 0.03 \)), and red cell folate (\( r = 0.04 \)) were not significant.

**Secondary outcomes.** Participants treated with vitamins declined less than placebo controls on the Digit Cancellation Test at 12 months (\( t = 2.10, p = 0.037 \)) and the CVLT immediate recall scores at 24 months (\( t = 1.97, p = 0.050 \) (table 3)). The groups did not differ on ITT analysis.

Finally, the groups did not differ with regards to the 4 mental summary scales of the SF-36: mental health (\( z = -1.31, p = 0.191 \)), vitality (\( z = -0.57, p = 0.572 \)), role emotional (\( z = 0.27, p = 0.790 \)), and social functioning (\( z = 0.79, p = 0.431 \)).

**Long-term outcomes.** Seventy-three men took part in the telephone interview with a mean age of 86 years and an average time to assessment of 7.7 years from the baseline study assessment. Men in the intervention group were 28% less likely to develop significant cognitive impairment than men in the placebo group (OR 0.72, 95% CI 0.25–2.09, \( p = 0.544 \)). Similar results were obtained after adjustment for age, baseline cognitive performance (as measured by the ADAS-cog), tHcy at baseline, depressive symptoms, education, and alcohol use (OR 0.66, 95% CI 0.2–2.24, \( p = 0.508 \)).
A total of 127 men died by the end of follow-up (mean time to death 7 years in both groups). Treatment with vitamins had no obvious effect on death hazard (HR 1.13, 95% CI 0.8–1.61, p = 0.477; HR 1.06, 95% CI 0.74–1.51, p = 0.751 after adjustment for confounding).

Thirty-four men had a recorded diagnosis of dementia on WADLS (including the 99 men who were alive and did not complete the TICS) or scored 27 or lower on the TICS (i.e., clinically significant cognitive impairment at follow-up). The odds of cognitive impairment associated with B-vitamin treatment was...
In the intervention group, total plasma homocysteine decreased compared with placebo (95% CI 0.29–1.78, p = 0.470). These results remained unchanged after adjustment for confounding.

**Biochemistry.** Total plasma homocysteine decreased by 22.5% (3.1 μmol/L) in the intervention group compared with a 10.7% (1.4 μmol/L) increase in the placebo group (t = −8.20, p < 0.001). Similarly, vitamin B₁₂ (306.2 vs 27.8 pmol/L, t = 13.01, p < 0.001) and red cell folate levels (747.1 vs 97.1 nmol/L, t = 11.06, p < 0.001) increased in the vitamin group compared with placebo. These results have been reported in greater detail elsewhere.³³

**Adverse events.** No significant adverse events were associated with treatment, and a similar proportion of participants discontinued participation in the study throughout the trial (28 in the vitamin group and 17 in the placebo group).

**Compliance with treatment.** Twenty-four–month compliance with treatment was 112/150 (74.7%) for men treated with vitamins and 112/149 (75.2%) for men treated with placebo (χ² = 0.01, p = 0.920). There was no difference between the groups in the primary outcome of interest when the data from only compliant men were reanalyzed (p = 0.602; data not shown).

**DISCUSSION** The results of this trial indicate that the use of vitamins B₆, B₁₂, and folate for 2 years does not change the rate of cognitive decline among men with hypertension aged 75 years or older. We did observe that, compared with placebo, treatment with vitamins was associated with fleeting gains on measures of immediate recall and attention, but those changes were not sustained over time. In addition, 2 years of B-vitamin supplementation did not seem to benefit these men in terms of mortality or a later diagnosis of dementia.

Before discussing our results, we wish to consider the merits and limitations of our study. We selected men aged 75 years or over with preexisting hypertension in order to test the effect of the intervention in a population that is at high risk of cognitive decline and impairment.³⁴ Participants were recruited from a well-established community representative sample of older men,³² and procedures for randomization and blinding were strictly adhered to. We performed both CCA and ITT analysis, loss to follow-up was low, and participants showed good compliance with treatment. Moreover, we maintained the intervention for an extended period of time (2 years) and recorded in WADLS, n = 19). The average follow-up time (time to event) was 8.3 years in both groups and treatment with vitamins was associated with a hazard ratio of 0.72 compared with placebo (95% CI 0.29–1.78, p = 0.470). These results remained unchanged after adjustment for confounding.

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**Table 2** Baseline characteristics of 299 older men randomly allocated placebo or homocysteine-lowering vitamin supplements

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 149)</th>
<th>Vitamins (n = 150)</th>
<th>Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>78.7 (2.7)</td>
<td>79.3 (2.8)</td>
<td>t = 1.97</td>
<td>0.050</td>
</tr>
<tr>
<td>Education: age left school, y, mean (SD)</td>
<td>15.1 (1.8)</td>
<td>15.1 (1.7)</td>
<td>t = 0.10</td>
<td>0.924</td>
</tr>
<tr>
<td>Harmful or hazardous alcohol use, n (%)</td>
<td>20 (13.4)</td>
<td>13 (8.7)</td>
<td>z = 1.72</td>
<td>0.189</td>
</tr>
<tr>
<td>BDI score, mean (SD)</td>
<td>6.3 (4.0)</td>
<td>6.1 (4.4)</td>
<td>z = −0.82</td>
<td>0.415</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L), mean (SD)</td>
<td>91.3 (35.5)</td>
<td>90.0 (23.9)</td>
<td>z = 0.84</td>
<td>0.400</td>
</tr>
<tr>
<td>Total plasma homocysteine (μmol/L), mean (SD)</td>
<td>13.1 (3.8)</td>
<td>14 (6.4)</td>
<td>z = 0.78</td>
<td>0.436</td>
</tr>
<tr>
<td>SF36–mental health, mean (SD)</td>
<td>84.8 (27.6)</td>
<td>85.1 (29.0)</td>
<td>z = 0.47</td>
<td>0.639</td>
</tr>
<tr>
<td>ADAS-cog, mean (SD)</td>
<td>11.8 (6.0)</td>
<td>11.0 (5.1)</td>
<td>z = −0.77</td>
<td>0.437</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>27.6 (1.9)</td>
<td>27.5 (1.8)</td>
<td>z = −0.99</td>
<td>0.325</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer’s Disease Assessment Scale; BDI = Beck Depression Inventory; CVLT = California Verbal Learning Test; MMSE = Mini-Mental State Examination.

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**Figure 2** Between-group comparisons of the change in cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) scores

Adjusted ADAS-cog change from baseline scores of men treated with B-vitamins and placebo over 24 months (intention-to-treat). The whiskers indicate the error bars of the mean change in ADAS-cog score at each timepoint. Mixed effects model showed that there was no difference between the groups overall (t = 0.28, p = 0.779).
treatment with vitamins was effective in reducing tHcy by 22.5%.

The trial was adequately powered to identify clinically relevant differences between the groups, but not mortality or dementia endpoints. We did not specifically recruit men with high tHcy or low serum concentration of vitamins, and this may have compromised the effect size of the intervention.

There are a number of plausible explanations as to why the seemingly strong association between cognitive impairment and elevated tHcy is not supported by the results of randomized trials. The duration of treatment in some trials may have been too short as some prospective studies have suggested that only prolonged exposure to elevated tHcy is associated with cognitive impairment. It is also possible that vitamin supplementation is more effective in people with some level of cognitive dysfunction, although our findings and those of others have not supported this view.

Published trials may have lacked power to investigate changes of cognitive scores that could be considered to be of clinical relevance, while others may have included people who were either too young or too old to benefit from treatment (i.e., cognitive changes take many years to become apparent and are more pronounced later in life or alternatively there is a critical risk period). Finally, observational surveys have generally shown that the association between tHcy and cognition is strongest with increasing tHcy, although no obvious differences emerged when our analyses were limited to men with tHcy ≥15 μmol/L.

The most economical explanation for our findings, however, is that elevated plasma homocysteine is not a risk factor but merely a marker that reflects underlying common processes responsible for both dementia and high tHcy, and that homocysteine-lowering treatment with B-vitamins does not affect the long-term cognitive function of people at risk.

**AUTHOR CONTRIBUTIONS**

Statistical analysis was conducted by Dr. A.H. Ford and Dr. H. Alfonso.

**DISCLOSURE**

Dr. Ford reports no disclosures. Dr. Flicker serves as Internal Medicine Editor for *Geriatrie Medicine*, Associate Editor for *BMC Geriatrics*, on the editorial board of the *Australian Journal on Ageing*, and as Editor of the Cochrane Dementia and Cognitive Impairment Group; and receives research support from Pfizer Inc. and NHMRC. Dr. Alfonso and J. Thomas report no disclosures. Dr. Clarinette serves on scientific advisory boards for Lundbeck Inc., Pfizer Inc., and Novartis; serves as an editorial advisor to *Geriatric Medicine in General Practice*; and estimates that 10% of his practice at Fremantle Hospital consists of cognitive testing. Dr. Martins serves as Senior Editor for the *Journal of Alzheimer’s Disease*; serves as a consultant for and holds stock in Alzhyme Ltd.; and receives research support from Commonwealth Scientific and Industrial Research Organisation (Australia). Dr. Almeida has received funding for travel from Blackmores Ltd.

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**REFERENCES**


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**Table 3** Changes from baseline in cognitive function measures, mean (SD)

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>6-Month ITT</th>
<th>12-Month ITT</th>
<th>18-Month ITT</th>
<th>24-Month ITT</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog placebo</td>
<td>−0.3 (4.5)</td>
<td>−0.4 (4.3)</td>
<td>−1.2 (4.1)</td>
<td>−1.2 (3.9)</td>
<td>−0.8 (4.2)</td>
</tr>
<tr>
<td>Intervention</td>
<td>0.4 (4.4)</td>
<td>0.3 (4.3)</td>
<td>−0.9 (3.9)</td>
<td>−1.0 (4.3)</td>
<td>0.1 (4.2)</td>
</tr>
<tr>
<td>CDT placebo</td>
<td>0.0 (0.5)</td>
<td>0.0 (0.6)</td>
<td>0.0 (0.6)</td>
<td>0.0 (0.6)</td>
<td>0.0 (0.6)</td>
</tr>
<tr>
<td>Intervention</td>
<td>0.0 (0.5)</td>
<td>0.0 (0.5)</td>
<td>−0.1 (0.6)</td>
<td>−0.1 (0.5)</td>
<td>0.0 (0.5)</td>
</tr>
<tr>
<td>CVLT 1 placebo</td>
<td>−3.7 (10.1)</td>
<td>−3.6 (9.8)</td>
<td>−3.5 (8.1)</td>
<td>−3.6 (7.7)</td>
<td>−3.6 (8.8)</td>
</tr>
<tr>
<td>Intervention</td>
<td>−4.2 (10.4)</td>
<td>−3.9 (10.2)</td>
<td>−4.2 (9.9)</td>
<td>−4.1 (9.5)</td>
<td>−4.2 (9.2)</td>
</tr>
<tr>
<td>CVLT 2 placebo</td>
<td>−0.8 (4.0)</td>
<td>−0.8 (3.8)</td>
<td>−0.3 (3.2)</td>
<td>−0.3 (3.0)</td>
<td>−0.2 (3.2)</td>
</tr>
<tr>
<td>Intervention</td>
<td>−0.8 (3.6)</td>
<td>−0.7 (3.5)</td>
<td>−0.5 (3.3)</td>
<td>−0.4 (3.2)</td>
<td>−0.6 (3.1)</td>
</tr>
<tr>
<td>MMSE placebo</td>
<td>−0.69 (1.77)</td>
<td>−0.7 (1.7)</td>
<td>0.0 (1.8)</td>
<td>0.0 (1.7)</td>
<td>−0.1 (1.8)</td>
</tr>
<tr>
<td>Intervention</td>
<td>−0.3 (2.0)</td>
<td>−0.3 (1.9)</td>
<td>0.0 (1.5)</td>
<td>0.0 (1.5)</td>
<td>0.1 (1.6)</td>
</tr>
<tr>
<td>DCT placebo</td>
<td>−0.5 (4.1)</td>
<td>−0.5 (3.9)</td>
<td>−0.5 (4.7)</td>
<td>−0.5 (4.5)</td>
<td>0.1 (4.3)</td>
</tr>
<tr>
<td>Intervention</td>
<td>−0.1 (5.2)</td>
<td>−0.2 (5.0)</td>
<td>0.8b (4.7)</td>
<td>0.7c (4.5)</td>
<td>0.3 (4.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer’s Disease Assessment Scale; CDT = Clock Drawing Test; CVLT 1 = California Verbal Learning Test List A immediate free recall trials 1–5 total; CVLT 2 = California Verbal Learning Test List A long-delay free recall; DCT = Digit Cancellation Test; ITT = intention-to-treat; MMSE = Mini-Mental State Examination.

* p = 0.050.

b p = 0.037.

c p = 0.015.


