Homocysteine Lowering and Cognition in CKD: The VA Homocysteine Study

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Abstract

Background—Individuals with advanced chronic kidney disease (CKD) and end stage renal disease (ESRD) have high total plasma homocysteine (tHcy) levels, which may be a risk factor for cognitive impairment. Whether treatment with high dose B-vitamins to reduce high tHcy levels improves cognition in persons with kidney disease is unknown.

Study Design—Randomized controlled trial.

Setting & Participants—A substudy of 659 patients (mean age 67.3 ± 11.7 years) who participated in a randomized, double-blind, clinical trial, 5 years in duration, conducted in 36 US Department of Veterans Affairs medical centers, of the effect on all-cause mortality of vitamin-induced lowering of plasma tHcy. 236 (35.8%) were treated by dialysis (ESRD) and 423 (64.2%) had a Cockcroft-Gault estimated creatinine clearance ≤ 30 ml/min (advanced CKD). All had high tHcy levels (≥15 μmol/L) at baseline. Cognitive assessments began during the follow up period of the main trial, 3 years after treatment began; participants were subsequently retested one year later to assess cognitive change.

Intervention—Daily high dose B-vitamin capsule (40 mg of folic acid, 100 mg of vitamin B6, and 2 mg of vitamin B12) or placebo.

Outcomes—Cognitive function at initial assessment and one year later.

Measurements—The Telephone Interview of Cognitive Status – modified, supplemented with attention, working memory and executive function tests.

Results—Initial cognitive function was impaired in approximately 19% of patients, regardless of treatment assignment (vitamin or placebo) or kidney disease status (advanced CKD or ESRD). Treatment reduced tHcy levels by 26.7%. Unadjusted and adjusted analyses showed that treatment did not improve initial cognitive outcomes or affect subsequent cognitive status one year later.

Limitations—Cognitive assessments began after treatment was initiated; cognitive assessment was limited.

Conclusion—Treatment with high daily doses of B-vitamins, which reduced tHcy levels, did not affect cognitive outcomes in patients with advanced CKD and ESRD.

Index Words

Cognition; Kidney Disease; Homocysteine; Clinical Trial

Introduction

Cognitive impairment and dementia are common in individuals with kidney disease [1-8]. They also have high total plasma homocysteine (tHcy) levels [9-11]. In observational studies of other populations, elevated tHcy levels have been associated with impairment and decline on tests of cognitive function [12-15], and have been implicated as an independent risk factor for dementia in cross-sectional, case-control [16] and prospective [17, 18] studies. A recent review [19] of clinical trials using B-vitamin therapy (B6, B12, and folic acid either alone or in vitamin combinations) to reduce tHcy levels, however, found little evidence that reducing tHcy improves cognitive outcomes.

Most previous clinical trials were conducted in relatively small samples with moderate elevation of tHcy levels, were of short duration, and employed low doses of vitamins; none was conducted in kidney disease patients who have high tHcy levels. We sought to address these limitations by examining whether high dose B-vitamin treatment for a long duration had a beneficial effect on cognitive outcomes in a large sample of individuals with advanced chronic kidney disease (CKD) or end stage renal disease (ESRD) and high levels of tHcy in the Department of Veterans Affairs (VA) Cooperative Studies Program Homocysteine Study (HOST) [20]. The present study examined cognitive function in a subset of these HOST participants.

Methods

Study Design

This was a substudy of the VA HOST Study, which was a 5-year multicenter randomized double blind placebo controlled clinical trial conducted from 2001 to 2006 in 36 VA medical centers. Details of the parent VA HOST study methods and the results have been reported previously [20, 21]. In brief, the objective of HOST was to determine if high daily doses of folic acid (40 mg), pyridoxine (vitamin B6, 100 mg) and cyanocobalamin (vitamin B12, 2 mg) to reduce tHcy would reduce all-cause mortality and improve cardiovascular outcomes compared to patients who received placebo. The primary inclusion criteria for the parent study were: age 21 years or older, advanced CKD (estimated creatinine clearance by Cockcroft-Gault[22] ≤ 30mL/min, n = 1305) or ESRD (n = 751), and high tHcy levels (≥15 μmol/L). Participants in HOST provided written informed consent.

At study entry, relevant medical history and laboratory data (including baseline fasting tHcy and B-vitamin levels) were collected and patients were given a three month supply of study drug. Patients returned in three months, and fasting tHcy and folate levels were collected, in addition to information about study outcomes. Subsequent patient contact occurred quarterly via telephone from two centers. The median follow-up interval was 3.2 years. Adherence was monitored by having patients return unused study drug when a new three-month supply arrived by mail from the research pharmacy. Among patients assigned to the vitamin treatment group in the HOST study, 90.3% reported taking study medication at 1 year, 87.6% at 2 years, and 85.3% at 3 years[21]. The results of the HOST Study showed that although the vitamin treatment lowered tHcy by 25.8%, it did not improve survival or reduce the incidence of cardiovascular events [21].

The aim of this cognitive function substudy was to assess whether treatment with high dose B-vitamins leading to tHcy reduction improved cognitive outcomes in a subset of HOST participants. Enrollment into the cognitive function substudy began in June, 2005 during the follow-up period of the parent HOST study (i.e., after enrollment into HOST was completed). Participants in the cognitive function substudy were administered a telephone cognitive battery and a mood questionnaire at enrollment into the substudy and one year later using identical methods. The follow-up calls were made within a four month window; 2 months before to 2 months after each participant's initial test anniversary. Because cognitive function fluctuates between hemodialysis treatments, with better performance seen within 24 hours since dialysis[23], we conducted the cognitive assessments in ESRD patients within 24 hours after their last dialysis. Calls were made by trained callers who were periodically assessed to maintain protocol adherence throughout the study. The Human Rights Committee at the VA coordinating center in West Haven and the Institutional Review Boards at the VA Boston Healthcare System and Stanford University approved the study.

Participants/Study Population

Potential participants from the parent HOST study were initially contacted by mail, with telephone follow up. Consent was obtained by telephone from those who agreed to participate and the cognitive battery and mood questionnaire were administered.

Cognitive/mood measures

Participants were administered a 20-minute battery of three cognitive tests and a mood questionnaire over the telephone. The *Telephone Interview for Cognitive Status – modified* (*TICSm*[24]) is a brief telephone cognitive assessment similar to the Mini-Mental State Exam (MMSE) that assesses orientation, concentration, memory (immediate and delayed word list recall), responsive naming, comprehension, calculation, reasoning and judgment. The

maximum score is 50 and a score of 27 or below is the usual cutoff for possible cognitive impairment [25, 26]. The test has been well-validated [24, 27, 28]. For this study, we added a forced-choice recognition trial after the delayed recall of the 10-item word list to further assess aspects of forgetfulness. *Digit span forward and backward* was adapted from the Wechsler Adult Intelligence Scale[29]; we administered one trial, rather than the traditional 2 trials at each span. The forward span measure is considered an index of attention, whereas the backward span measure is an index of working memory[30]. *Verbal fluency* was used as an executive function measure, and was assessed by asking the participant to name as many different animals as possible in 60 seconds. *The Geriatric Depression Scale – Short Form*[31] (GDS-SF) was used to assess mood, given the importance of assessing depressed mood when examining cognition in patients with kidney disease[32]. The GDS-SF is a series of 15 yes/no questions addressing aspects of depressed mood. We selected the GDS-SF because it is easily administered over the telephone, has been well-validated in numerous older adult populations[33], and has fewer items focusing on somatic complaints that result in over-estimating depressive symptoms in patients with kidney disease [32].

Outcomes

Cognition was assessed according to three primary outcomes collected at substudy enrollment-- the TICSm total score and separate cognitive and memory composites. The cognitive composite was composed of scores from the TICSm, digit span forward and backward, and verbal fluency. We constructed the cognitive composite by converting the score from each cognitive measure (TICSm total score, digit span forward and backward span scores, and verbal fluency) into z-scores based on each score's respective mean and standard deviation from the entire sample at initial testing. The four z-scores were then averaged to create the cognitive composite z-score. The memory composite was constructed similarly using the word list memory items from the TICSm. We converted the scores for the immediate and delayed recall trials, and the recognition trial to z-scores in a similar fashion as above. We averaged the three memory scores to create the memory composite z-score.

A secondary outcome, cognitive change, was a categorical variable (improve, decline, no change) that was based on the change in TICSm performance over a one-year interval. Estimating true change on cognitive measures is complicated by measurement error and retest effects that occur in repeated administrations of a test. To account for these effects, we calculated a reliable change index (RCI)[34] which estimated the degree of change over repeated administrations of the TICSm that exceeded what would be expected due to measurement error and/or retest effects[35, 36]. In a manner similar to selecting rejection regions, or *P values*, for statistical tests[34], we selected upper (i.e., true improvement) and lower (i.e., true decline) cutoff regions equivalent to a two-tailed test at *P* < 0.1. Accordingly, an RCI of -1.65 or lower represented reliable decline, an RCI of 1.65 or higher represented reliable improvement, and RCIs between these values represented no change over 1 year (the RCI formula and calculations are provided as Item S1 of the online supplementary material available with this article at www.ajkd.org).

Statistical Analyses

All treatment effects were analyzed according to the randomized treatment groups regardless of adherence. Our analyses of the three cognitive outcomes at initial testing were based on comparing unadjusted mean differences between the placebo and treatment group by t-tests. Subsequent adjusted analyses of treatment group differences at initial testing included relevant baseline covariates and used a priori multiple linear regression models, with follow-up post hoc models based on the initial model results. Prespecified treatment by kidney disease status (advanced CKD, ESRD) interaction tests were performed to examine whether treatment effects on cognition varied as a function of kidney disease status. Chi-square analyses were used to

examine treatment group differences in categorical baseline covariates and 1-year change (i.e., RCI) in TICSm performance. Statistical significance was set at P = 0.05 for a two-tailed test for all statistical analyses.

Results

Enrollment in the parent HOST study began in September 2001; enrollment in the cognitive function substudy began in June 2005 and continued until July 2006; annual retests were completed by June 2007. Figure 1 illustrates the timing of the enrollment and follow-up periods for the cognitive function substudy and parent HOST study. At the inception of the cognitive function substudy, 1375 participants were still active in the HOST study. Of those, 659 were recruited into the substudy, 236 with ESRD and 423 with advanced CKD. The differences in baseline characteristics at enrollment into the HOST study between those in the substudy and in the remainder of HOST participants that are statistically significant were, respectively: age (63.7 vs. 66.7 years), past history of myocardial infarction (20.5% vs. 27.0 %), congestive heart failure (17.9% vs. 26.5 %), angina (20.0% vs. 27.6 %), stroke (12.0% vs. 16.7 %), presence of diabetes (50.5% vs. 57.2%), body mass index (28.1 vs. 27.6), and diastolic blood pressure (75.4 mmHg vs. 73.8 mmHg). Otherwise, the characteristics of the cognitive function participants were similar to the characteristics of those not enrolled in the substudy.

There were 320 participants in the placebo group and 339 in the vitamin group (Figure 2) in the cognitive function study subsample. Baseline data (at HOST randomization) of the participants enrolled in the substudy by treatment group are presented in Table 1. The vitamin group had a lower rate of antiplatelet use, fewer strokes and higher hemoglobin values at baseline; otherwise the two groups were similar.

In May 2006 the Data and Safety Monitoring Board recommended the parent HOST study be halted early because the required number of primary endpoints (deaths) had occurred. All participants in HOST stopped taking the study drug and the parent study ended August 31, 2006. Although all participants underwent initial cognitive testing while still taking the study drug, 454 of the 490 participants who were retested had discontinued the drug before being retested. There were no differences between the groups for the mean length of treatment (placebo, 1144 days; vitamin, 1128 days, $P = 0.4$). The double blind was not broken, and the results of the parent HOST study were not given to participants until after the final cognitive retest had occurred.

Treatment effects on tHcy and B-vitamin levels

During the parent HOST study, baseline and 3-month median tHcy levels for the treatment and placebo groups in the cognitive substudy were as follows: vitamins, 22.5 μmol/L and 16.5 μmol/L ($P < 0.001$); placebo, 22.2 μmol/L and 21.1 μmol/L ($P = 0.09$). Over the same interval, median folate levels for the treatment and placebo groups were as follows: vitamins, 15.9 ng/mL and 2050.0 ng/mL ($P < 0.001$); placebo, 14.8 ng/mL and 17.1 ng/mL ($P = 0.004$). These treatment results were similar to those in the parent study[21]. The mean interval between enrollment in HOST and enrollment in the substudy was 3.1 years for both the vitamin and placebo groups; thus, those in the vitamin group had been treated for 3.1 years before being tested.

Treatment effects on cognitive outcomes at initial testing

There were no differences between placebo and vitamin groups on any cognitive measure or outcome, or on the GDS-SF (Table 2). We also examined whether there were differences in the prevalence of cognitive impairment between the groups, using a TICSm score of 27 or

below as the cutoff for impairment [25, 26], and found that the rates of impairment were similar (placebo, 17.5%; vitamin, 20.7; P = 0.3).

Vitamin treatment had no effect on any cognitive outcome in models adjusted for the following variables collected at HOST baseline: demographic information, kidney disease status (advanced CKD, ESRD), cardiovascular disease, diabetes, blood pressure, hypertension treatment, and tHcy and GDS-SF score at the time of cognitive testing (Table 3). Baseline tHcy was negatively associated only with TICSm performance; follow-up analyses determined that this association was not related to baseline levels of folate and B-vitamins (P values ranged from .09 to 0.9). Cognitive outcomes were not significantly different for advanced CKD compared to ESRD participants at baseline or during follow-up (i.e., adjusted for the dialysis status at the time of initial testing in this substudy; P values ranged from 0.07 to 0.9) and there were no significant treatment by kidney disease status interactions on any cognitive outcome (P values ranged from 0.6 to 0.9). Although there were significant baseline differences between the treatment groups in stroke rate and hemoglobin level (Table 1), neither was significantly related to the cognitive outcomes in our models (P values ranged from 0.1 to 0.9).

Prevalence of cognitive impairment at initial testing

We further examined the prevalence of cognitive impairment at initial testing using a TICSm score of 27 or below as the cutoff for impairment. Prevalence rates were similar across kidney disease groups (advanced CKD, 18.7%; ESRD, 19.9%; P = 0.7); these rates did not change when we performed subsequent analyses adjusted for the dialysis status at the time of initial testing in this substudy to account for any effects of change in kidney disease status from baseline. The prevalence of cognitive impairment increased by age decade (collapsed across kidney disease status) as follows: 40s, 3.4%; 50s, 10.9%; 60s, 14.0%; 70s, 28.2%; 80s, 28.7% (P < 0.001).

Treatment effects on 1-year change in TICSm performance

One-year retests were completed in 490 participants. Retests were not conducted on 169 participants because of: loss to follow-up (73), death (72), refusal (20), and illness or confusion (4). The proportions of those who were not retested were similar in the placebo and vitamin groups, 25% (80/320) and 27% (92/339), respectively. There were no effects of treatment on 1-year change on the TICSm at the RCI cutoffs of +/- 1.65 (Table 4). Follow-up sensitivity analyses using RCI cutoffs that were either more liberal (i.e., +/- 1.29) or conservative (i.e., +/- 1.96) also were nonsignificant (P values = 0.9 in both cases).

Discussion

Treatment with high daily doses of folic acid and vitamins B_6 and B_{12} reduced tHcy levels by 26.7%, and the reduction was maintained for over three years[21]. However, in this subset of participants, treatment did not influence cognitive outcomes at initial testing or change in cognition over a 1-year interval. These findings do not support the administration of B-vitamin therapy to improve cognitive outcomes in persons with advanced CKD and ESRD.

Our findings confirm the null findings of other clinical trials of the effects of B-vitamin therapy or tHcy reduction on cognitive outcomes in other populations [19, 37-41], and extend these findings to advanced CKD and ESRD patients with higher baseline tHcy values receiving a higher dose B-vitamin intervention than those in previous studies. In contrast, the Folic Acid and Carotid Intima-Media Thickness (FACIT) trial cognitive substudy [42], found that tHcy reduction via daily administration of 800 μg of folic acid improved cognitive outcomes in a large sample of community-dwelling older adults. It is unclear why the FACIT study found a

beneficial effect of tHcy reduction on cognition whereas other similarly designed studies [38, 39] did not.

Two other notable findings were that the advanced CKD and ESRD groups had similar rates (approximately 19%) of cognitive impairment on the TICSm, and that cognitive impairment was present in nearly a third of patients aged 70 and older. In comparison, previous studies found that the prevalence of cognitive impairment was between 15-20% in advanced CKD [1-3, 43]. The prevalence of cognitive impairment in our ESRD sample was lower than the 27-87% prevalence seen in similar studies [1, 5, 44-46], and may be due to differences in sample composition (e.g., age, comorbid conditions) or the cognitive measures used. The higher cognitive impairment prevalence in older members of our sample confirms recent findings about cognitive impairment in an aging CKD population [8, 47].

There are several explanations for the failure to find a treatment effect on cognitive outcomes in our study. First, our participants had a high comorbidity burden of hypertension, diabetes and vascular disease. These comorbidities affect cognition [48-51], and may have obscured any treatment effect on cognition. Second, although tHcy levels were reduced by 26.7%, only a third of the participants had their tHcy levels reduced to normal levels of 8 - 10 μmol/L[21]. The results of the FACIT trial[42] suggested that tHcy may need to be lowered into the normal range to produce beneficial effects on cognition; however, McMahon et al.[39] reduced tHcy to normal levels in their trial and found no cognitive effect of this reduction.

Several limitations of this study may have contributed to the failure to demonstrate a treatment effect on cognition. The lack of baseline measurement of cognitive function at initial randomization in the parent study is an important limitation. However, two other trials examining cognitive function decline also enrolled a cohort during the follow up period of the main study; one found treatment effects on cognition[52] whereas another did not[53]. Because of this design limitation, we assumed that baseline cognitive function was similar in the two treatment groups at randomization, and any differences at the initial cognitive function assessment at 3 years after randomization would be due to treatment effects. It is likely that cognitive function was similar across the treatment groups at baseline because the groups did not differ in risk factors for cognitive dysfunction, such as age or hypertension, but it cannot be known for certain.

Moreover, we could not determine whether cognitive decline occurred in the 3-year interval between enrollment into HOST and the cognitive substudy. Thus, we may not have detected a treatment effect because our sample may have been cognitively stable during this interval. There are two reasons why this latter possibility is unlikely. First, although longitudinal data about cognitive function in CKD are limited, a significant decline has been demonstrated over 2-4 year intervals in both CKD[54] and ESRD[55] patients. For example, Kurella-Tamura[54] showed that those with moderate to advanced CKD (i.e., estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m^2) were nearly 2.5 times more likely to decline over 4 years on the Modified Mini Mental State Exam (3MS; decline defined as either a decline of > 5 points, or 1 standard deviation, or a score that decreased to < 80) compared with those without CKD (i.e., eGFR ≥ 60 mL/min/1.73 m^2). Second, cognitive decline over a similar interval is related to increasing age[56-58] and vascular disease risk factors such as those present in our sample[59] in relatively healthier community-dwelling samples. Therefore, it is likely that cognitive decline would have occurred in the participants after initial randomization and before enrollment into the substudy. The participants enrolled in the cognitive function substudy represent a survivor cohort, since sicker patients would have died prior to initiation of the substudy. This possibility is reflected in the younger age and lower rates of vascular disease in the substudy participants. Nevertheless, risk factors for cognitive decline were balanced by

treatment group in the substudy participants and the burden of vascular comorbidities was still high.

Telephone assessment of cognition may not be as sensitive as an in-person interview to detect effects of treatment, but in-person assessments have also failed to disclose cognitive benefits of tHcy reduction[39]. The early discontinuation of the parent HOST trial may have contributed to our not finding treatment effects over a one-year duration; however, since there were no differences in initial cognitive assessment after 3 years of treatment, it is unclear why discontinuing treatment would effect a change over one year. We were not able to conduct 1-year retests on 169 participants. Although the loss of follow-up data from these participants could have introduced bias into our 1-year retest results, it is unlikely that this affected the treatment effect results because the proportion of those who were not retested was similar in the placebo (25%) and vitamin (27%) groups. Finally, this trial was conducted in the United States after folic acid fortification of the food supply was completed in 1998, which may have reduced the power to detect the effect of folic acid intervention on cognition[60, 61].

In summary, we found a high prevalence of cognitive impairment in a large cohort of patients with advanced CKD and ESRD. The prevalence of cognitive dysfunction increased with age, with 28% of those over the age of 70 years having cognitive impairment. Treatment with high daily doses of B-vitamins, which reduced tHcy levels, did not improve cognitive outcomes compared to placebo and should not be recommended for treatment or prevention of cognitive dysfunction in patients with advanced CKD or ESRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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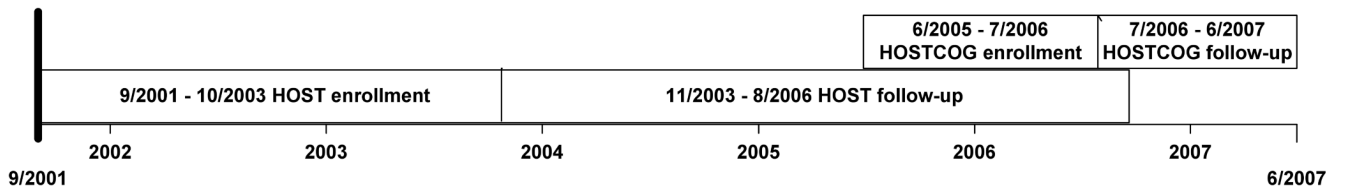
Figure 1.
Veterans affairs (VA) Homocysteine Study (HOST) and VA Homocysteine Study Cognitive Function Substudy (HOSTCOG) enrollment and follow-up timelines.
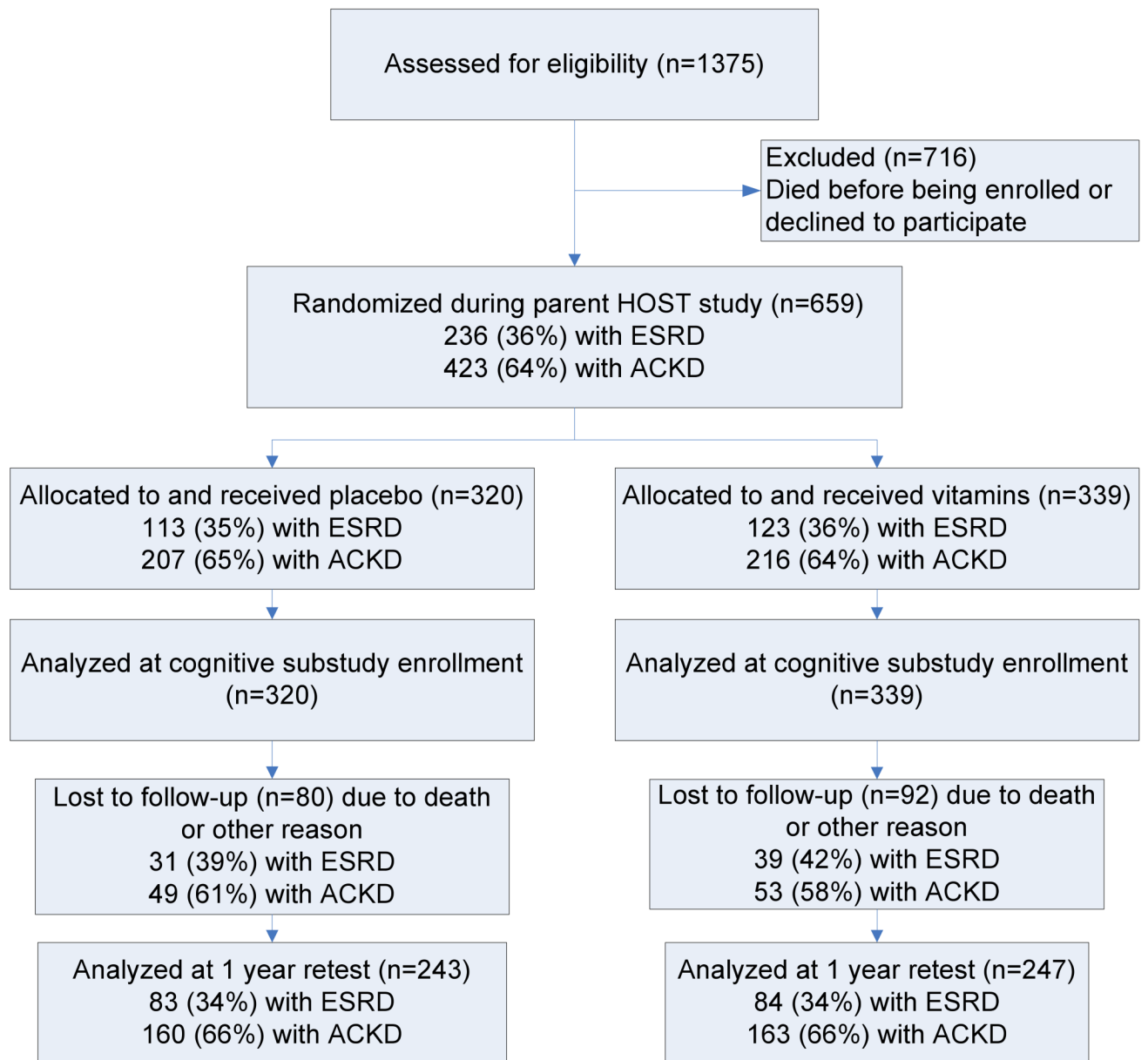
Figure 2.
Flow of participants into the Veterans Affairs Homocysteine Study (HOST) Cognitive Function Substudy. Abbreviations: ESRD, end stage renal disease; ACKD, advanced chronic kidney disease.

Table 1

Baseline Characteristics[*] of HOST Cognitive Function Substudy Population Assigned to Placebo vs. Vitamins

Characteristic	Placebo (n = 320)	Vitamins (n = 339)	P value
Age, mean (SD), y	64.2 (11.2)	63.2 (12.2)	0[ND1].3
Men, No. (%)	315 (98.4)	333 (98.2)	0.8
Racial/ethnic group, No (%)			0.3
White, non-Hispanic	164 (51.2)	159 (46.9)	
African American, non-Hispanic	110 (34.4)	136 (40.1)	
Hispanic	40 (12.5)	34 (10.0)	
Other or missing information	6 (1.9)	10 (3.0)	
Smoking status, No. (%)			0.8
Never	88 (27.5)	87 (25.7)	
Former	177 (55.3)	189 (55.8)	
Current	55 (17.2)	63 (18.6)	
Body mass index, kg/m^2, mean (SD)[†]	28.2 (5.0)	28.0 (4.8)	0.5
Systolic blood pressure, mean (SD), mm Hg	140.2 (24.0)	142.9 (21.7)	0.1
Diastolic blood pressure, mean (SD), mm Hg	74.5 (13.2)	76.3 (12.9)	0.08
Medical history, No (%)			
Myocardial infarction	67 (20.9)	68 (20.1)	0.8
Congestive heart failure	57 (17.8)	61 (18.0)	0.9
Hypertension	308 (96.2)	330 (97.4)	0.4
Angina	58 (18.1)	74 (21.8)	0.2
Percutaneous coronary angioplasty or stenting	39 (12.2)	41 (12.1)	0.9
Coronary artery bypass graft surgery	49 (15.3)	49 (14.4)	0.8
Stroke	47 (14.7)	32 (9.4)	0.04
Diabetes mellitus	167 (52.2)	166 (49.0)	0.4
Concommitant medication use, No. (%)			
β-Blockers	188 (58.8)	192 (56.6)	0.6
Calcium channel blockers	199 (62.2)	207 (61.1)	0.8
Lipid-lowering agents	163 (50.9)	152 (44.8)	0.1
Aspirin or antiplatelet agents	138 (43.1)	121 (35.7)	0.05
ACE inhibitors	141 (44.1)	152 (44.8)	0.8
Angiotensin II receptor blockers	39 (12.2)	35 (10.3)	0.5

Laboratory values, mean (SD)

Characteristic	Placebo (n = 320)	Vitamins (n = 339)	*P* value
Hemoglobin, g/dL	11.8 (1.7)	12.2 (1.6)	<0.001
Albumin, g/dL	4.0 (0.5)	4.0 (0.5)	0.9
Total cholesterol, mg/dL	168.8 (40.0)	169.6 (40.6)	0.8
HDL cholesterol, mg/dL	42.2 (16.7)	42.2 (12.3)	0.9
LDL cholesterol, mg/dL	91.5 (31.6)	93.3 (33.2)	0.5
Triglyerides, mg/dL	183.1 (128.4)	180.8 (150.9)	0.8

Note: Conversion factors for units: hemoglobin and albumin in g/dL to g/L, x10; total, HDL, and LDL cholesterol in mg/dL to mmol/L, x0.0259; triglycerides in mg/dL to mmol/L, x0.0113.

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*
Values at baseline of parent Homocysteine Study.

†
Body mass index was calculated as weight in kilograms divided by height in meters squared.

Table 2

Cognitive Function Measures at Initial Assessment Among Participants Assigned to Placebo vs. Vitamins

Cognitive Measure	Placebo	Vitamins	*P* value
TICSm	32.1 (5.2)	31.8 (5.1)	0.5
Digit span forward – span	5.6 (1.6)	5.6 (1.4)	0.8
Digit span backward – span	3.8 (1.4)	3.7 (1.3)	0.3
Verbal Fluency	15.7 (5.3)	16.2 (4.8)	0.2
Global cognition z-score composite	0.003 (0.8)	-0.009 (0.7)	0.8
Memory z-score composite	0.003 (0.8)	-0.005 (0.8)	0.9
Geriatric Depression Scale	3.4 (3.3)	3.5 (3.3)	0.6

Note. Values expressed as mean± SD

Abbreviation: TICSm, Telephone Interview for Cognitive Status – modified

Table 3

Association Between Baseline Homocysteine, Vitamin Treatment, and Cognitive Outcomes in Adjusted Models Using Multiple Regression[*]

Cognitive Outcome	Baseline Homocysteine (µmol/L)[†]		Vitamin Treatment[‡]	
	Regression coefficient (*SE*)	*P* value	Regression coefficient (*SE*)	*P* value
TICSm	-.05 (.02)	.04	-.28 (.34)	0.4
Cognitive composite	-.00 (.00)	.4	-.01 (.05)	0.9
Memory composite	-.00 (.00)	.6	-.02 (.06)	0.7

Note: Homocysteine reported in umol/L, unit for conversion to mg/L, x0.135. Cognitive composite = Cognitive z-score composite composed of TICSm totals score, digit span forward and backward span scores, and verbal fluency total correct. Memory composite = Memory composite composed of TICSm word list immediate and delayed recall, and the recognition trials.

Abbreviations: TICSm = Telephone Interview of Cognitive Status – modified, *SE* = standard error

[*] Models adjusted for the following variables collected at HOST baseline: age, education, race, kidney disease status (advanced chronic kidney disease, end-stage renal disease), cardiovascular disease, diabetes, systolic and diastolic blood pressure, hypertension treatment, and plasma total homocysteine. Geriatric Depression Scale score at the time of cognitive testing was also included in the model.

[†] Values at baseline of parent VA Homocysteine Study.

[‡] Effect of vitamin treatment compared with placebo.

Table 4

1-year Change on TICSm Among Participants Assigned to Placebo vs. Vitamins

RCI	Placebo	Vitamins
Improve	19	23
Decline	20	22
No change	204	202

Note: 490 participants completed Time 2 assessments. Improve = 1-year TICSm improvement of 6 or more points. Decline = 1-year TICSm decline of 5 or more points. No change = TICSm 1-year differences between these values.

There were no differences between placebo and vitamin groups in the number of participants who improved, declined or showed no change on the TICSm over a 1-year interval via Chi-Square analyses, $P = 0.8$.

Abbreviations: TICSm = Telephone Interview for Cognitive Status – modified, RCI = Reliable Change Index.