HHS Public Access

Author manuscript

J Ren Nutr. Author manuscript; available in PMC 2015 April 27.

Published in final edited form as:

J Ren Nutr. 2012 March ; 22(2): 268–76.e1-3. doi:10.1053/j.jrn.2011.07.009.

Cognitive dysfunction and depression in adult kidney transplant recipients: Baseline findings from the FAVORIT Ancillary Cognitive Trial (FACT)

Aron M. Troen, D.Phil.[1,2,7], **Tammy Scott, Ph.D.**[5], **Kristen E. D'Anci, Ph.D.**[1], **Denish Moorthy, M.D.**[1], **Beverly Dobson, M.P.A.**[1], **Gail Rogers, M.A.**[4], **Daniel E. Weiner, M.D. M.S.**[6], **Andrew S. Levey, M.D.**[6], **Gerard E Dallal, Ph.D.**[3], **Paul F. Jacques, Sc.D.**[4], **Jacob Selhub, Ph.D.**[2], **Irwin H. Rosenberg, M.D.**[1], and **for the FACT Study Investigators**[**]

[1]Nutrition and Neurocognition Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston MA

[2]Vitamin Metabolism and Aging Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston MA

[3]Biostatistics Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston MA

[4]Nutritional Epidemiology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston MA

[5]Department of Psychiatry, Tufts Medical Center and Tufts School of Medicine, Boston, MA

[6]Division of Nephrology, Tufts Medical Center and Tufts School of Medicine, Boston MA

[7]Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Israel

Abstract

Objective—Hyperhomocysteinemia and B-vitamin deficiency may be treatable risk factors for cognitive impairment and decline. Hyperhomocysteinemia, cognitive impairment and depression all are common in individuals with kidney disease, including kidney transplant recipient. Accordingly, we assessed the prevalence of cognitive impairment and depressive symptoms in transplant recipients and their association with kidney function, plasma total homocysteine (tHcy) and B-vitamin concentrations.

Corresponding Author: Aron Troen, D. Phil., Nutrition and Brain Health Laboratory, Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel, Phone ++972-8-948-9476, aron.troen@tufts.edu.

[**]See appendix A

No other authors have financial interests to disclose.

Setting—Cross sectional analysis of baseline data from the FAVORIT Ancillary Cognitive Trial, which included 183 participants in FAVORIT who underwent detailed neuropsychological assessment prior to the study intervention.

Results—The mean age was 54.0 ± 9.5 yrs (range 7–386 months). Men comprised 55.2% of the cohort and the mean time between the current transplant and cognitive testing was 7.0 ± 5.8 yrs. 24% of participants reported neurological or psychiatric complaints and 30% exhibited symptoms of mild to severe depression. Testing revealed evidence of significant and selective deficits in this population: 33% performed more than 1 SD below normed means on a memory test, 58% fell lower than 1 SD below the norms on a test of attention and mental processing speed, and 33–42% fell lower than 1 SD below the norms on several tests of executive function. Lower estimated glomerular filtration rate and lower folate were associated with poorer performance on tests of memory and executive function.

Conclusions—These observations confirm previous reports of mood and cognitive impairments in adult kidney transplant recipients. Further research is needed to determine the benefit of B-vitamin supplementation and other interventions in this patient population.

Keywords

Transplantation; Cognition; Depression; Homocysteine; B-vitamins

INTRODUCTION

In the general population, mild elevations of plasma total homocysteine (tHcy) are associated with cognitive impairment and increased risk of incident dementia [1–4]. These associations are hypothesized to reflect homocysteine-induced cerebrovascular damage or the inhibition of B-vitamin-dependent methylation activity in the brain [5–7].

Kidney transplant recipients are a unique population in which to assess the relationship between hyperhomocysteinemia, B-vitamin levels and cognitive function. This reflects the high prevalence of hyperhomocysteinemia in individuals with chronic kidney disease (CKD) as well as the favorable long term prognosis of most kidney transplant recipients that requires greater clinical emphasis on diagnosis and management chronic diseases like dementia. Elevations of tHcy in kidney transplant recipients are often in the range associated with increased risk of cerebrovascular disease and cognitive decline in the general population [8]. It is uncertain why hyperhomocysteinemia is such a prominent feature of CKD. Following transplant, homocysteine levels are typically lowered although not normalized, and they can be further lowered through high-dose B-vitamin therapy [9]. The association among tHcy, B-vitamin status and cognitive function in the transplant population remains unknown.

Cardiovascular disease is a major source of morbidity and the most common cause of death following kidney transplantation, with event rates two to four-fold higher than expected based on population estimates [10, 11]. Theoretically, elevated tHcy may account for some of the increased cardiovascular disease risk in this population [12], and, until recently, was an attractive potential target of therapeutic interventions to reduce the cardiovascular disease

burden in CKD patients, given that hyperhomocysteinemia typically responds to high-dose B-vitamin therapy. While the past decade has witnessed large clinical trials of B-vitamin therapy to reduce cardiovascular disease and mortality in individuals with CKD, these have largely been disappointing [13, 14]. Similar trials in the general population have also demonstrated no significant impact of B-vitamin therapy on cardiovascular disease and all-cause mortality, despite significant lowering of tHcy associated with B-vitamin therapy [15]. However, with respect to neurocognitive outcomes, some trials have yielded evidence of beneficial effects of B-vitamin therapy for cognition and prevention of brain atrophy [16–18]. Thus, at a minimum, tHcy remains an attractive biomarker for cardiovascular and cerebrovascular risk and, potentially, it may remain a target for prevention, albeit requiring the identification of individuals most likely to benefit from B-vitamin therapy [19, 20] or the use of non-vitamin based strategies in individuals at risk.

The Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT, NIH NIDDK UO1 DK61700) is a randomized, double blinded, controlled trial that tests the hypothesis that treatment with B-vitamin therapy to lower tHcy will reduce the rate of CVD outcomes in stable kidney transplant recipients [9]. The FAVORIT Ancillary Cognitive Trial (FACT-R01 DK65114) was conducted on a subset of the FAVORIT study population to prospectively determine whether there was an effect of B-vitamin therapy to lower homocysteine on cognition. In the current study, we describe the relationship of baseline tHcy levels and B-vitamin levels to cognitive function, including depressive symptoms, in 183 FACT participants who were evaluated upon randomization into FAVORIT.

PARTICIPANTS AND METHODS

Study Population

The FAVORIT trial, a multicenter, randomized, double-blind controlled clinical trial among clinically stable kidney transplant recipients who have mild to moderately elevated tHcy levels, was designed to determine whether lowering tHcy with high-dose B-vitamin treatment reduces the pooled occurrence of recurrent and *de novo* non-fatal and fatal arteriosclerotic outcomes, including coronary heart, cerebrovascular, and peripheral vascular disease events [9]. Detailed methods and baseline characteristics have been published elsewhere [9, 21]. Eligible volunteers were 35 to 75 years old and were required to have a functioning kidney allograft of at least 6-months, mildly elevated screening random/non-fasting tHcy level (≥12 μmol/L for men and ≥11 μmol/L for women), and estimated creatinine clearance (Ccr) ≥30 mL/min derived with the Cockroft-Gault equation [22]. After July 2005, the Ccr eligibility criterion was decreased to ≥25 mL/min in women.

FACT is a longitudinal ancillary to FAVORIT to determine whether there is an effect of B-vitamin treatment on cognitive performance. The study was implemented at 20 of the 30 sites in FAVORIT with a recruitment goal of at least 1000 FAVORIT participants (appendix A). As the initiation of FAVORIT predated the initiation of FACT by more than a year, FAVORIT participants were eligible for FACT at either the time of randomization or the time of an annual follow-up visit. The only exclusion criteria for FACT were visual or hearing impairment substantial enough to hinder performance on cognitive testing. The FACT protocol was approved by the Tufts Medical Center Institutional Review Board and

by the Institutional Review Boards at each participating study site. Of 1349 participants who enrolled in FACT, 195 enrolled in FACT at the time of FAVORIT randomization, and 183 of these underwent in-person cognitive testing. These participants comprise the baseline group for this analysis.

Demographic and Laboratory Data Ascertainment

Most demographic and clinical data were ascertained from FAVORIT study materials. Additional, self-reported demographic variables were collected for FACT, including years of formal education; past or present neurological symptoms that may be associated with decreased kidney function; and use of psychotropic and antidepressant medication. Archived baseline blood was available for biochemical assays of 171 of the 183 subjects who underwent cognitive testing at baseline. tHcy (N=169) was measured by high-performance liquid chromatography (HPLC) [23]. Serum creatinine (N=171) was determined by a kinetic adaptation of the Jaffe reaction on a Cobas Mira Analyzer, Roche Diagnostic Systems, Inc., Indianapolis, IN, with estimated glomerular filtration rate (eGFR) calculated using the 4-variable Modification of Diet in Renal Disease Study (MDRD) equation based on serum creatinine assays before calibration to isotope dilution mass spectrometry [24]. Folate and B12 (N=171) were measured using the Quantaphase II radioassay kit (Bio-Rad Laboratories, Hercules, CA). Pyridoxal 5'-phosphate (vitamin B6; N=170) was determined by the tyrosine decarboxylase apoenzyme method [25].

Cognitive testing

A battery of well-validated neuropsychological tests was administered in person during participants' FAVORIT clinic visits. These tests were selected to evaluate multiple domains of cognition and mood, including memory, executive function, processing speed and depression [26–28]. Research staff at participating FAVORIT clinics were trained in test administration at bi-annual training sessions held at Tufts University, with on-site sessions occurring as needed to ensure consistent and valid testing procedures. The cognitive battery is presented in Table 1. Raw test scores were converted to age and sex-adjusted scaled scores (age, sex and education-adjusted T-scores for the Trail Making tests) to facilitate comparison with published population based norms. As cognitive impairment is often associated with disorders of mood, *depressive symptoms* were evaluated using the Center for Epidemiological Studies Depression Scale (CES-D) questionnaire, a common non-diagnostic screening tool that gauges the severity of self-reported symptoms of depression during the week before testing. In general population samples, a score of less than 16 is not consistent with depression, while a score of 16 to 21 indicates potential mild to moderate depression, and a score of 22 or greater is potentially consistent with major depression [29].

Statistical analyses

All variables were checked for normalcy, and skewed variables including folate and tHcy were log transformed. Raw cognitive test scores were converted to age-adjusted scaled-scores for the Word List Learning, Block Design and Digit Symbol tests, and were converted to age, sex and education adjusted t-scores for the Trails Making tests. Impairment was defined by scores more than one standard deviation below the norm [30].

The significance of divergence between the observed and expected distribution of cognitive scores was determined by a one-sided one-sample binomial test and effect size was calculated by Cohen's d [31].

Cross sectional baseline associations between between cognitive scores and tHcy, B-vitamins, and kidney function were calculated in 3 models using simple and partial correlation coefficients for tHcy and B-vitamins adjusting for age, sex, and education, as well as eGFR. For memory scores where score distributions indicated possible ceiling effects, the analyses were confirmed by TOBIT and Logistic regression. To avoid collinearity, we did not include B-vitamins in models where tHcy was the predictor, and vice versa. Analyses were performed with SPSS version 15.0 (SPSS, Inc., Chicago, IL) and SAS version 9.1.3 (*SAS* Institute Inc, Cary, NC).

RESULTS

There were 183 FACT participants who underwent cognitive assessment at the time of randomization in FAVORIT, 13 of whom had undergone more than one kidney transplant. The mean time between the current transplant and cognitive testing was 7.X ± 5.8 years (range 7 – 386 months) The mean age of FACT participants was 54.0 ± 9.5 years; men comprised 55.2% of the cohort and 27% were African American and 69.7% were Caucasian. Overall, participants in this cohort were well-educated: 72.7% reported that they obtained some advanced education beyond high school; 21.3% hold a bachelor or associate degree and 8.2% hold a graduate or professional degree. The prevalence of diabetes was 41%, and the prevalence of cardiovascular disease was 17.5% including 6.6% with a history of stroke (Table 2). These data are similar to baseline data in FAVORIT participants not initially participating in FACT [21]. Baseline plasma tHcy concentrations were mildly elevated, with a mean of 15.4 ± 5.5 μmol/L and range of 7.7–39.3 μmol/L, and baseline GFR was 49.6 ± 20.2 mL/min/1.73m^2. Plasma tHcy was highly correlated with creatinine with eGFR ($r = -0.47$, $P < 0.001$). In contrast, plasma tHcy was weakly correlated with vitamin B12 ($r = -0.17$, $P = 0.03$), and was not correlated with either folate or vitamin B6 (Table 3).

Mean estimated pre-morbid intelligence was slightly above average, with a Verbal IQ score of 104.3 ± 12.6. Approximately one out of four subjects reported one or more of the neurological or psychiatric conditions listed in Table 4. A self-report of any current condition was associated with significantly higher Verbal IQ scores (109.7 ± 9.1 vs. 102.6 ± 13.0, $P < 0.05$) but not with worse cognitive function. Notably, self-reported memory lapses were not predictive of performance on the Word List Learning test.

Neuropsychiatric testing revealed evidence of significant deficits and substantial depressive symptoms in this population. These selectively affected specific cognitive domains. There was poor encoding of new information (immediate recall on the Word List Learning test) but normal retention of information that was learned (percent retention on the word learning list). In addition, the Digit Symbol Coding and Trail Making tests revealed significant psychomotor slowing and executive dysfunction. In contrast, performance on the Block Design test showed that visuospatial organization was not affected (Table 5). In a normal population, 15.8% of individuals would perform at 1 standard deviation (SD) or more below

the norm. In this population we find that 33% of subjects perform below the 1 SD cutoff for Word List Learning immediate recall, 58% perform below this cutoff on the Digit Symbol test, and 42% and 33% are below the cutoff for Trails A&B respectively. These deficits are all the more striking given that verbal IQ, retention of information and visuospatial organization were all at expected levels or better (Table 5). In keeping with the prevalence of self-reported depression (9.3%), the CES-D questionnaire revealed a high prevalence of frequent depressive symptoms. 18.6% of all subjects were classified as mildly depressed (16<=CES-D <22), and 11.3% as severely depressed (CES-D >=22). Self-reported depression was associated with significantly higher CES-D scores (19.0 ± 11.4 vs. 11.1 ± 8.2, P <0.01) but not with any other cognitive outcome.

Homocysteine was not significantly associated with any cognitive measure. However it is notable that the correlation of homocysteine with executive function (Trails B) changed from r=0.02 in model 2 to r=0.16 in model 3 when eGFR was adjusted for in addition to age, sex and education (Table 6). Higher blood folate concentration was associated with better memory scores (percent retention, r=0.20; Recognition; r=0.19; P <0.05) and with better executive function (Trails B; r=−0.21, P <0.05) after adjusting age, sex, education and eGFR. Worse kidney function was also associated with worse executive function (Trails B; r=0.25, P <0.01).

DISCUSSION

Cognition and depression in adult kidney transplant recipients has received scant attention in the literature. Nevertheless, there is evidence to suggest that the cognitive risks that are associated with chronic kidney disease [32] will also apply to transplant recipients who typically have at least a moderate degree of kidney function impairment. In the Cardiovascular Health Study which evaluated an elderly community-based cohort, moderate kidney function impairment at baseline (defined as serum creatinine ≥1.5 mg/dL for men and ≥1.3 mg/dL for women) in subjects otherwise reporting good to excellent health was associated with significantly greater risk of incident vascular but not Alzheimer's type dementia over mean follow up period of six years [33]. In the current study, mean creatinine levels for both men and women (Table 2) are even higher than those predictive of risk in the Cardiovascular Health Study, suggesting that this population of kidney transplant recipients may be at similar risk for progressive cognitive decline. Recent baseline findings in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) show that the carotid stenosis and pulse wave velocity may be increased in chronic renal disease to an extent generally seen in individuals 10–15 years older [34]. Although, the ASFAST study did not assess cognition, such accelerated carotid aging is predictive of cognitive decline [35]. More recently, a cross sectional study in 23,405 participants (mean age, 64.9 +/− 9.6 years) of the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study reported an 11% increase in the prevalence of cognitive impairment for every 10 mL/min/1.73 m^2 decrease in eGFR below than 60 mL/min/1.73 m^2 [36]. The majority of our population falls below this range (Table 2).

Consistent with this prediction, our baseline findings indicate that kidney transplant recipients experience functionally significant, but selective, decrements in cognitive

function. Executive function (Trails tests) and mental processing speed and attention (Digit Symbol Coding) are particularly affected while other cognitive domains such as memory may be relatively spared. Although these cognitive domains are not strictly independent, selective impairments in attention and processing speed on the Digit Symbol Coding and the Trails tests are often associated with subcortical cerebrovascular lesions [26, 37] whereas memory impairment tends to be more closely associated with cortical and medial temporal lesions [38, 39]. In some cases, depression may also have a cerebrovascular origin [5, 40]. Thus, the observed pattern of deficits and depression in this population is consistent with incipient cerebrovascular disease. Indeed, at 6.6%, the prevalence of cerebrovascular disease in this cohort is considerably higher than a population-based expected value of 0.6% [41]. Such cerebrovascular disease is likely to manifest with subtle and progressive cognitive impairments [37].

Our findings of cognitive impairment in this baseline subset of the FACT cohort represent the largest study to date of cognition in adult kidney transplant recipients. Comparable published data are limited. Gelb et al., (2008) assessed cognition in 42 kidney transplant recipients, 45 outpatients with pre-dialysis CKD and 49 healthy controls and found significantly worse verbal learning and memory among transplant and CKD patients in comparison to controls. They also found a non-significant decrement in the Trails test of the same magnitude as in our study; however they were underpowered to detect statistical significance [42]. Although we too found cognitive impairment in transplant recipients and a similar pattern of executive dysfunction, verbal learning and memory were unimpaired in our cohort. Griva *et al*. (2004) evaluated cognition in 117 British kidney transplant recipients and 145 hemodialysis patients and compared their performance with normative reference data [30]. In their study, the mean age for transplant recipients in the of 50.3 ± 12.3 years was 6 years younger than in the present study with a similar sex ratio of 59.8% male to 40.2% female. Educational achievement was slightly lower (11.2 ± 3.8 years), with longer duration of dialysis before transplantation (2.6 ± 2.7 years) and a similar duration of transplant (8.6 ± 6.6 years). Similar neuropsychological tests were administered including the digit symbol-coding and trails tests, while the Rey auditory verbal learning test (RAVLT) and the grooved pegboard tests were used instead of the word list and block design tests. Griva et al. found transplant recipients to have considerably better cognition compared to hemodyalisis patients suggesting that transplantation can partially reverse the deficits that are associated with renal insufficiency. However, while performance on the Trails A and B, Digit Symbol Coding and RAVLT among transplant recipients was close to the norm, performance was 0.55–0.77 standard deviations below the norm on the Grooved Pegboard tests. That the overall cognitive deficits were milder when compared to ours might be due in part to the comparatively lower mean age and education in Griva et al.'s study. Moreover, while the authors concluded that their cohort was unimpaired, their focus was on the improvement in transplantation vs. hemodialysis, and their relatively stringent criterion for impairment was an average decrement of 1 SD below the norm. By the same criterion, we find that more subjects underperform than would be expected for a normal population, particularly in view of our cohort's above average verbal IQ and memory function. Although we cannot exclude the possibility that these deficits were present in the pre-morbid condition, cognitive function is typically highly correlated across cognitive domains. It

would therefore be unusual to observe such a discrepancy between domains in the absence of an underlying pathology.

While relatively subtle, such impairments are clinically meaningful and carry risk of further deterioration over time [43–45]. The association of lower function in multiple cognitive domains with lower folate but not with homocysteine is consistent with a mechanism whereby folate affects cognitive function independently of homocysteine [46]. The lack of association with homocysteine may be partly explained by the fact that homocysteine is more closely related to kidney function than to B-vitamins in this population (Table 3). The relation of kidney disease to cognitive function by other mechanisms may obscure that of homocysteine to cognition [47].

Depression is another important issue in this population. Depression is prevalent in end-stage renal disease [48] but the prevalence of depression in kidney transplant recipients with functioning grafts is uncertain [49–52]. The high prevalence of depressive symptoms in this cohort (18.6% mild and 11.3% severe) suggests that, although cognition may be partially restored following transplantation, depression may be less amenable to correction by transplantation [51]. The lack of correlation of depressive symptoms with eGFR, B-vitamins or tHcy in this cohort is inconsistent with findings in the general population [53, 54]. Depression affects health outcomes in many chronic diseases. Thus further characterization of depression and its causes in kidney transplant recipients will be important for treating and improving quality of life in this population [50].

A limitation of the FACT study is that participants of the FAVORIT parent trial can decline to volunteer for the ancillary cognitive study. This raises a potential concern of selection bias, in that those who are worried about their cognition may be more likely to participate or decline. Although we can not exclude this possibility, it is unlikely given that subjective self-reported memory complaints did not correlate with memory or other cognitive scores on neuropsychological testing. Moreover, the baseline characteristics of our baseline sample were not different from the baseline characteristics of the parent trial [21].

FACT is designed to determine whether treatment with B-vitamins will benefit cognition and mood in adult kidney transplant recipients, compared to treatment with placebo. Upon completion of the study, FACT will also make it possible to examine additional determinants of cognition and mood in this population. In conclusion, the cognitive characteristics of this cohort suggest that close attention should be paid to cognition and mood in caring for adult kidney transplant recipients, regardless of homocysteine levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SUPPORT AND FINANCIAL DISCLOSURES

This research was supported by grant RO1 DK65114 and cooperative agreement UO1 DK61700 from the from the National Institute of Diabetes and Digestive and Kidney Diseases with additional financial support from the Office

of Dietary Supplements, National Institutes of Health, Department of Health and Human Services, and by cooperative research agreement 58-1950-4-401 with the U.S. Department of Agriculture. Jacob Selhub has consulted for Pam Lab LLC of Covington, LA.

REFERENCES

1. Clarke R, Smith AD, Jobst KA, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 1998; 55(11):1449–1455. [PubMed: 9823829]
2. Kado DM, Karlamangla AS, Huang MH, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. Am J Med. 2005; 118(2):161–167. [PubMed: 15694902]
3. Riggs KM, Spiro A 3rd, Tucker K, et al. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. Am J Clin Nutr. 1996; 63(3):306–314. [PubMed: 8602585]
4. Troen A, Rosenberg I. Homocysteine and cognitive function. Semin Vasc Med. 2005; 5(2):209–214. [PubMed: 16047273]
5. Bertsch T, Mielke O, Holy S, et al. Homocysteine in cerebrovascular disease: an independent risk factor for subcortical vascular encephalopathy. Clin Chem Lab Med. 2001; 39(8):721–724. [PubMed: 11592441]
6. Sachdev P. Homocysteine, cerebrovascular disease and brain atrophy. J Neurol Sci. 2004; 226(1–2): 25–29. [PubMed: 15537514]
7. Selhub J, Bagley LC, Miller J, et al. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr. 2000; 71(2):614S–620S. [PubMed: 10681269]
8. Bostom AG, Gohh RY, Beaulieu AJ, et al. Treatment of hyperhomocysteinemia in renal transplant recipients. A randomized, placebo-controlled trial. Ann Intern Med. 1997; 127(12):1089–1092. [PubMed: 9412311]
9. Bostom AG, Carpenter MA, Kusek JW, et al. Rationale and Design of the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) Trial. American Heart Journal. 2006 In Press.
10. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med. 1988; 84(6):985–992. [PubMed: 3287917]
11. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998; 32(5):853–906. [PubMed: 9820460]
12. Bostom AG, Culleton BF. Hyperhomocysteinemia in chronic renal disease. J Am Soc Nephrol. 1999; 10(4):891–900. [PubMed: 10203375]
13. Brady CB, Gaziano JM, Cxypoliski RA, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. Am J Kidney Dis. 2009; 54(3):440–449. [PubMed: 19628319]
14. Mann JF, Sheridan P, McQueen MJ, et al. Homocysteine lowering with folic acid and B vitamins in people with chronic kidney disease--results of the renal Hope-2 study. Nephrol Dial Transplant. 2008; 23(2):645–653. [PubMed: 18003666]
15. Loscalzo J. Homocysteine trials--clear outcomes for complex reasons. N Engl J Med. 2006; 354(15):1629–1632. [PubMed: 16531615]
16. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007; 369(9557):208–216. [PubMed: 17240287]
17. Scheltens P, Kamphuis PJ, Verhey FR, et al. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimers Dement. 2010; 6(1):1–10. e1. [PubMed: 20129316]
18. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 2010; 5(9):e12244. [PubMed: 20838622]

19. Spence JD. Perspective on the efficacy analysis of the Vitamin Intervention for Stroke Prevention trial. Clin Chem Lab Med. 2007; 45(12):1582–1585. [PubMed: 17937609]
20. Spence JD, Bang H, Chambless LE, et al. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. Stroke. 2005; 36(11):2404–2409. [PubMed: 16239629]
21. Bostom AG, Carpenter MA, Hunsicker L, et al. Baseline characteristics of participants in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial. Am J Kidney Dis. 2009; 53(1):121–128. [PubMed: 19022547]
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31–41. [PubMed: 1244564]
23. Araki A, Sako Y. Determination of free and total homocysteine in human plasma by high-performance liquid chromatography with fluorescence detection. J Chromatogr. 1987; 422:43–52. [PubMed: 3437026]
24. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007; 53(4):766–772. [PubMed: 17332152]
25. Shin YS, Rasshofer R, Friedrich B, et al. Pyridoxal-5'-phosphate determination by a sensitive micromethod in human blood, urine and tissues; its relation to cystathioninuria in neuroblastoma and biliary atresia. Clin Chim Acta. 1983; 127(1):77–85. [PubMed: 6825312]
26. Dufouil C, Alperovitch A, Ducros V, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol. 2003; 53(2):214–221. [PubMed: 12557288]
27. Ramos MI, Allen LH, Haan MN, et al. Plasma folate concentrations are associated with depressive symptoms in elderly Latina women despite folic acid fortification. Am J Clin Nutr. 2004; 80(4): 1024–1028. [PubMed: 15447915]
28. Duthie SJ, Whalley LJ, Collins AR, et al. Homocysteine, B vitamin status, and cognitive function in the elderly. Am J Clin Nutr. 2002; 75(5):908–913. [PubMed: 11976166]
29. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. Applied Psychological Measurement. 1977:1385–1401.
30. Griva K, Hansraj S, Thompson D, et al. Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data. Nephrol Dial Transplant. 2004; 19(7):1866–1874. [PubMed: 15150346]
31. Cohen, J. Statistical power analysis for the behavioral sciences. 2nd ed.. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
32. Weiner DE. The cognition-kidney disease connection: lessons from population-based studies in the United States. Am J Kidney Dis. 2008; 52(2):201–204. [PubMed: 18640482]
33. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol. 2004; 15(7):1904–1911. [PubMed: 15213280]
34. Zoungas S, Kerr PG, Chadban S, et al. Arterial function after successful renal transplantation. Kidney Int. 2004; 65(5):1882–1889. [PubMed: 15086931]
35. Rao R. The role of carotid stenosis in vascular cognitive impairment. J Neurol Sci. 2002:203–204. 103–107.
36. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. 2008; 52(2):227–234. [PubMed: 18585836]
37. Jokinen H, Kalska H, Mantyla R, et al. Cognitive profile of subcortical ischaemic vascular disease. J Neurol Neurosurg Psychiatry. 2006; 77(1):28–33. [PubMed: 16361588]
38. Jokinen H, Kalska H, Ylikoski R, et al. Medial temporal lobe atrophy and memory deficits in elderly stroke patients. Eur J Neurol. 2004; 11(12):825–832. [PubMed: 15667413]
39. van der Flier WM, Middelkoop HA, Weverling-Rijnsburger AW, et al. Neuropsychological correlates of MRI measures in the continuum of cognitive decline at old age. Dement Geriatr Cogn Disord. 2005; 20(2–3):82–88. [PubMed: 15942197]
40. Thomas AJ, Perry R, Kalaria RN, et al. Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. Int J Geriatr Psychiatry. 2003; 18(1):7–13. [PubMed: 12497551]

41. Kannel, W.; Gordon, T. The Framingham Study: an epidemiological investigation of cardiovascular disease. Washington, DC: Department of Health, Education, and Welfare; 1977. p. 94-103.
42. Gelb S, Shapiro RJ, Hill A, et al. Cognitive outcome following kidney transplantation. Nephrol Dial Transplant. 2008; 23(3):1032–1038. [PubMed: 18065801]
43. Palmer K, Fratiglioni L, Winblad B. What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. Acta Neurol Scand Suppl. 2003; 179:14–20. [PubMed: 12603245]
44. Palmer K, Wang HX, Backman L, et al. Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. Am J Psychiatry. 2002; 159(3):436–442. [PubMed: 11870008]
45. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999; 56(3):303–308. [PubMed: 10190820]
46. Antoniades C, Shirodaria C, Leeson P, et al. MTHFR 677 C>T Polymorphism reveals functional importance for 5-methyltetrahydrofolate, not homocysteine, in regulation of vascular redox state and endothelial function in human atherosclerosis. Circulation. 2009; 119(18):2507–2515. [PubMed: 19398669]
47. Weiner DE, Bartolomei K, Scott T, et al. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Am J Kidney Dis. 2009; 53(3):438–447. [PubMed: 19070412]
48. Finkelstein FO, Wuerth D, Troidle LK, et al. Depression and end-stage renal disease: a therapeutic challenge. Kidney Int. 2008; 74(7):843–845. [PubMed: 18794813]
49. Akman B, Ozdemir FN, Sezer S, et al. Depression levels before and after renal transplantation. Transplant Proc. 2004; 36(1):111–113. [PubMed: 15013316]
50. Kimmel PL, Peterson RA. Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. Semin Dial. 2005; 18(2):91–97. [PubMed: 15771651]
51. Overbeck I, Bartels M, Decker O, et al. Changes in quality of life after renal transplantation. Transplant Proc. 2005; 37(3):1618–1621. [PubMed: 15866689]
52. Tossani E, Cassano P, Fava M. Depression and renal disease. Semin Dial. 2005; 18(2):73–81. [PubMed: 15771649]
53. Sachdev PS, Parslow RA, Lux O, et al. Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. Psychol Med. 2005; 35(4):529–538. [PubMed: 15856723]
54. Tolmunen T, Hintikka J, Voutilainen S, et al. Association between depressive symptoms and serum concentrations of homocysteine in men: a population study. Am J Clin Nutr. 2004; 80(6): 1574–1578. [PubMed: 15585771]

Table 1

Neuropsychological Test Battery

	Cognitive Test	Scoring	Test Details
Intelligence	North American Adult Reading Test	128.7 - (0.89 * # of pronunciation errors)	Estimation of verbal intelligence quotient that requires subjects to read a list of 61 words out loud.
Supraspan Learning & Word Recall	Immediate Recall	Total initially correct	Subjects attempt to memorize a list of 12 words read out loud over 4 trials. After a delay of 25 to 35 minutes, *percent retention* is the percentage of words correctly recalled compared to *immediate recall* and *delayed recognition* is the number of words correctly identified as familiar or non-familiar from a list of 24.
	Percent Retention	Percent recall after delay	
	Delayed Recognition	Number of correctly identified words	
Visual Construction & Fluid Reasoning	Block Design	Number completed weighted for time	Subjects are required to reproduce depicted patterns using a set of colored blocks.
Attention, Mental Processing Speed, & Executive Function	Digit Symbol- Coding	Number of copied symbols in 2 minutes	Symbols are decoded by matching a given symbol to a digit provided in an answer key
	Trail Making Test A	Time to Completion	“Connect-the-dots” for a consecutive number sequence from 1 to 25.
	Trail Making Test B	Time to Completion	“Connect-the-dots” alternating between numbers (1 to 13) and letters (A to L) (ex: 1-A-2-B-3-C).
Mood	Center for Epidemiological Studies Depression Scale (CES-D) questionnaire	Self-reported symptoms of depression on a scale of 1–5	A total score of < 16 is not consistent with depression. A score of 16 to 21 indicates potential mild to moderate depression A score of >= 22 is potentially consistent with major depression

Table 2

Demographics and Study Parameters

N(%)	**183 (100%)**
Age at Exam (years)	54 ± 9.5
Duration of current transplant (years)	7 ± 5.8
tHcy (μmol/L)	15.4 ± 5.5
Creatinine (μmol/L)	141.4 ± 61.9
Folate (nmol/L)	41.2 ± 26.7
Vitamin B6 (nmol/L)	28.1 ± 27.6
Vitamin B12 (pmol/L)	482 ± 364
eGFR (mL/min/1.73m^2)	49.6 ± 20.2
Stage 1 CKD / eGFR 90+ (%)	4.7%
Stage 2 CKD / eGFR 60 – 89 (%)	19.4%
Stage 3 CKD / eGFR 30 – 59 (%)	60.0%
Stage 4 CKD / eGFR 15 – 29 (%)	15.9%

Table 3

Correlations between Homocysteine, Folate, B Vitamins, and Kidney Function

	tHcy	Folate	B12	B6	Creatinine	eGFR
tHcy	1	−0.15	−0.17*	−0.01	0.5**	−0.47**
Folate		1	0.12	0.36**	0.07	−0.12
B12			1	0.07	−0.03	−0.03
B6				1	−0.03	0.13
Creatinine					1	−0.76**

*$P < 0.05$,

**$P < 0.01$

J Ren Nutr. Author manuscript; available in PMC 2015 April 27.

Table 4

Self-Reported Neurological and Neuropsychiatric Conditions

Currently suffers from (self-reported):	%
Depression	9.3
Neuropathy	10.9
Memory Lapses	4.9
Confusion	2.2
Other	5.5
One or more of the above	24.0

Table 5

Baseline Cognitive Function in FACT participants in Comparison to Population Norms

	Adjusted scores Mean ± SD	Departure from Norm	Percent impaired (more than 1 SD below norm)	Cohen's d (Effect Size)	Percentile Standing[§]
Word List - Immediate Recall[a]	9.1 ± 3.6	−0.29 SD	33.3[*]	−0.27	39.4
Word List – Percent Retention[a]	11.9 ± 2.6	0.61 SD	4.4	0.68	75.2
Word List – Recognition[a]	10.3 ± 2.9	0.09 SD	12.6	0.10	54.0
Block Design[a]	10.1 ± 3.0	0.05 SD	16.9	0.03	51.2
Digit Symbol[a]	7.3 ± 3.3	−0.91 SD	57.9[*]	−0.86	19.5
Trails A[b]	42.6 ± 10.9	−0.74 SD	42.1[*]	−0.71	23.9
Trails B[b]	44.6 ± 9.9	−0.54 SD	32.8[*]	−0.54	29.5

[a] Age adjusted scaled-scores (Norm is a mean of 10, and standard deviation of 3).

[b] Age and sex adjusted t-scores (Norm is a mean of 50, and standard deviation of 10).

[*] Proportion impaired is significantly different than expected by one-sample binomial test (In a normal distribution, 15.8% of subjects are expected to fall below 1 standard deviation of the mean), $P < 0.05$.

[§] Effect size calculated according to Cohen's d allows the percentile of mean observed score to be calculated as a function of the population norm. For example, the mean score of FACT participants for Word List Percent Retention is at the 75. 2 percentile, whereas the mean Digit Symbol Coding Score is at the 19.5th percentile of the population norm.

Table 6

Partial Correlations of Homocysteine, Folate, and Kidney Function with Cognitive Tests Using Raw Scores

Model: **Adjusted for:** **Cognitive tests**	**Unadjusted**			**Model 2 Age, Sex and Education**			**Model 3 Model 2 + eGFR**	
	Ln(Folate)	**Ln (tHcy)**	**eGFR**	**Ln(Folate)**	**Ln (tHcy)**	**eGFR**	**Ln(Folate)**	**Ln (tHcy)**
Word List - Immediate Recall	**0.18***	−0.03	−0.10	0.14	−0.13	0.06	0.15	−0.11
Word List - Percent Retention[a]	**0.16***	0.06	**−0.16***	**0.20***	0.03	−0.05	**0.20***	0.01
Word List – Recognition[a]	0.15	0.03	−0.05	**0.18***	−0.04	0.05	**0.19***	−0.02
Block Design	0.11	−0.01	−0.13	0.11	−0.03	−0.13	0.10	−0.10
Digit Symbol	0.15	−0.10	−0.04	0.09	−0.11	0.03	0.10	−0.11
Trails A[b]	−0.08	−0.00	0.13	−0.09	0.05	0.07	−0.08	0.09
Trails B[b]	**−0.25****	0.08	**0.22****	**−0.23****	0.02	**0.25****	**−0.21***	0.16
CES-D	−0.07	−0.08	0.06	−0.08	0.01	−0.01	−0.08	0.00

[a] Memory score distributions showed possible ceiling effect. See Supporting Information confirming the significance of the association between folate and memory scores using TOBIT and LOGISTIC regressions that take this distribution into account.

[b] Trails scores are logged

* $P < 0.05$,

** $P < 0.01$