FGF-23 and Cognitive Performance in Hemodialysis Patients

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Abstract

Although cognitive impairment is common in hemodialysis (HD) patients, the etiology of and risk factors for its development remain unclear. Fibroblast growth factor 23 (FGF-23) levels are elevated in HD patients and are associated with multiple adverse outcomes including increased mortality and left ventricular hypertrophy. Despite FGF receptors being present throughout the brain, there are no prior studies which have assessed whether FGF-23 levels are associated with cognitive performance.

We measured FGF-23 levels in 263 prevalent hemodialysis patients in whom comprehensive neuro-cognitive testing was also performed. The cross-sectional association between patient characteristics and FGF-23 levels were assessed using multivariable linear regression. Principal factor analysis was used to derive two factors from cognitive test scores, representing memory and executive function, which by definition carried a mean of zero and standard deviation of one. Multivariable linear regression adjusting for age, sex, education status as well as other relevant covariates was used to explore the relationship between FGF-23 and each measure of cognitive function.

The mean age of participants was 63 years, 46% were women and 22% were African American. The median FGF-23 level was 3098 RU/ml (25^{th}-75^{th} percentile, 1139-7960 RU/ml). Younger age, lower prevalence of diabetes, longer dialysis vintage and higher levels of calcium and phosphorus were independently associated with higher FGF-23 levels. Higher FGF-23 was independently associated with a lower composite memory score [per doubling of FGF-23, beta = -0.08 SD (95% CI -0.16, -0.01)] and highest quartile versus lowest quartile, [beta = -0.42 SD (-0.82, -0.02)]. There was no definite association of FGF 23 with executive function when examined as a continuous variable [beta=-0.03 SD (-0.10, 0.04)], however there was a trend in the quartile analysis [beta=-0.28 SD (-0.63, 0.07), p=0.11, for 4^{th} quartile versus 1^{st} quartile].

FGF-23 was independently associated with worse performance on a composite memory score, even after adjustment for potential confounders, including measures of mineral metabolism. High FGF-23 levels in hemodialysis patients may contribute to cognitive impairment within this population.

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DISCLOSURES

No authors have financial conflicts related to this manuscript.

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Introduction

1.1 Background on Fibroblast growth factor 23 and Cognition

Recent studies demonstrate a high prevalence of cognitive impairment in patients with end-stage renal disease (ESRD).[1-3] Cognitive impairment adversely impacts multiple areas of patient care including patient compliance with treatment plans, quality of life, and mortality[3-5]; therefore, understanding its pathogenesis is essential to improving outcomes for patients with ESRD. A limited number of studies have evaluated risk factors for cognitive impairment in ESRD, and found that traditional cardiovascular disease risk factors like blood pressure, hyperglycemia and dyslipidemia do not fully explain the high risk of cognitive impairment in this population.[6,7]

Fibroblast growth factor 23 (FGF-23) is a phosphaturic hormone, whose levels increase as kidney function declines.[8] FGF-23 is associated with adverse outcomes including left ventricular hypertrophy (LVH),[9,10] vascular calcification,[11,12] incident cardiovascular events[13,14] and mortality in all stages of CKD.[13,15-17] Through an extra-renal pathway involving stimulation of fibroblast growth factor receptors, FGF-23 may cause direct end organ toxicity, particularly within cardiac muscle.[18] As FGF receptors are also found throughout the brain,[19,20] we hypothesized that FGF-23 may also promote neurotoxicity (Figure 1).

There are few studies investigating factors associated with FGF-23 levels in hemodialysis patients and no studies of which we are aware which have evaluated the relationship between FGF-23 and cognitive function. We therefore evaluated both the cross sectional relationship of patient characteristics with FGF-23 levels, and the association of these levels with detailed measures of cognitive function in prevalent hemodialysis patients.

1.2 Background on Asymmetric dimethylarginine and Cognition

Asymmetric dimethylarginine (ADMA) is a potent inhibitor of nitric oxide synthesis. Nitric oxide is a vasodilator involved in regulation of vascular resistance, and decreases in nitric oxide are associated with accelerated atherosclerosis[21-23]. ADMA is elevated in CKD and has been implicated as one possible mediator of vascular disease in this population[21,24]. Elevated levels of ADMA are associated with increased arterial stiffness, increased carotid artery thickness, and decreased cerebral blood flow[25,26]. Higher ADMA levels in dialysis patients are also associated with higher cardiovascular event rates, increased incidence of brain white matter disease, and higher mortality rates[27-29]. We therefore hypothesized that ADMA may be associated with decreased cognitive performance in hemodialysis patients through a pathway of increased cerebrovascular disease (Figure 1). There are no prior studies of which we are aware that have evaluated the relationship of ADMA to cognitive function.

Materials and Methods

2.1 Patient Population

Patients receiving chronic in-center hemodialysis at five Dialysis Clinic Inc. (DCI) units and one hospital based unit (St Elizabeth's Medical Center) in the greater Boston area were evaluated using previously described criteria for entry into the Cognition and Dialysis Study.[2] Reflecting the nature of the cognitive battery, eligibility criteria included English fluency as well as sufficient visual and hearing acuity to complete cognitive testing. To minimize cognitive testing floor effects and reflecting inability to provide consent, individuals with MMSE score $\leq$ 10 and/or advanced dementia based on medical record review were excluded. Non vascular access related hospitalization within 1 month, delirium, receipt of hemodialysis for less than 1 month, and single pool Kt/V <1.0 were temporary exclusion criteria. The Tufts Medical Center/Tufts University Institutional Review Board approved the study and all participants who underwent cognitive testing signed informed consent forms. The clinical and research activities being reported are consistent with the Declaration of Helsinki.

Demographic, clinical and laboratory characteristics were ascertained at the time of study enrollment. Demographic data (age, sex, and race) were obtained via participant report, review of medical charts, and the DCI and St. Elizabeth's Medical Center databases. Education (<12th grade, high school graduate, and $\geq$ 2 years of college) and smoking history (never, current or past smoker) were obtained via a standardized patient questionnaire. Medical history including history of cardiovascular disease (a composite of either a history of coronary artery disease or peripheral vascular disease), stroke and presence of diabetes were defined by patient history or documentation in the patient's electronic or paper charts. Additionally, DCI electronic medical records and paper records were reviewed for a history of these conditions with specific focus on problem lists, hospital discharge summaries, and cardiac testing results. The cause of ESRD and time since start of hemodialysis (dialysis vintage) were obtained from the DCI or St. Elizabeth's electronic record, as were the mean monthly pre-dialysis systolic and diastolic blood pressures. Pre-dialysis blood tests including hematocrit, phosphorus, calcium, white blood cell

count, C-reactive protein, albumin, and single pool Kt/V were obtained. Vitamin D 25 hydroxy levels were measured at a later date from stored frozen samples taken at study enrollment. All DCI laboratory tests were measured in a central laboratory in Nashville, TN.

2.2 FGF-23

FGF-23 levels were measured in singlicate from serum samples which had been stored at -80 degrees Celsius, after a single freeze–thaw cycle, in batched assays at the University of Maryland School of Medicine. Persons performing the testing were blinded to any patient clinical characteristics or outcomes. A c-terminal FGF-23 assay (Immutopics) was used as this method has been shown previously to be highly correlated with assays of the intact FGF-23 molecule.[17] This assay has a sensitivity of 1.5 relative units per ml (RU/ml) and inter-assay and intra-assay coefficients of variation of less than 5%.

2.3 ADMA

Samples were available for testing in 257 patients. Each sample was collected pre-dialysis, centrifuged, frozen at -80 Celsius and had not been previously thawed prior to testing. ADMA was measured in singlicate by high performance liquid chromatography[30] in batched assays at the University of Padua, Italy. Control samples were run with each batch to assess the reproducibility of test results. The coefficient of variation for control samples was 5.5%, similar to previously reported results using this method[31].

2.4 Cognitive assessment

Participants were administered a battery of cognitive tests by research assistants following training and direct observation by the study neuropsychologist (TMS). To maintain quality and inter-rater reliability, testing was observed by the study neuropsychologist at 3-6 month intervals. To limit subject fatigue, all testing was completed during the 1st hour of hemodialysis. The neuropsychological battery included well-validated commonly used cognitive tests that possess high inter- and intra-rater reliability and have established age, sex, and/or education-matched normative scores. The MMSE[32] was used as a screening test and the North American Adult Reading Test (NAART) served as a measure of premorbid verbal IQ.[33]

The neurocognitive battery consisted of the Wechsler Memory Scale-III (WMS-III) Word List Learning Subtest,[34] the Wechsler Adult Intelligence Scale-III (WAIS-III) Block Design and Digit Symbol-Coding Subtests,[34] and Trail Making Tests A and B[35] (Trails A and B). During the last two years of the study, the cognitive panel was expanded to include additional verbal tests assessing both memory and executive functions, including Digit Span (forwards and backwards),[34] the Mental Alternations Test,[36] and the Controlled Oral Word Association Test (COWAT).[37] The overall battery assesses a broad range of functioning including global ability, supraspan learning, auditory retention, visual retention, attention/mental processing speed, visual construction/fluid reasoning, and motor speed (Table 5).

2.5 Principal Factor Analysis

To limit multiple testing as well as address collinearity between cognitive tests, principal factor analysis with varimax rotation was used as a data reduction technique.[38] As previously reported in a recent study with the same cohort of patients, we obtained two principal factors on a larger group of 292 patients.[2] The first factor was termed "memory function" and the greatest contributing tests were the Word List Learning Recall and Recognition (Table 6). The second factor represented "executive functioning" or attention and processing speed as the Trails A and B, Block Design, and Digit Symbol-Coding tests were the largest contributors. By definition, each standardized factor has a mean of zero and a standard deviation of one, with higher scores indicating better cognitive performance.

2.6 Statistical Analyses

FGF-23

Descriptive characteristics of the study population were reported as proportions for categorical and binary variables, means with standard deviations for continuous normally distributed variables, and medians with inter-quartile ranges for skewed variables. To better assess differences across FGF-23 level, the study population was sorted into equally sized quartiles. Linear trends across quartiles were assessed

using linear regression used for continuous variables and the Cochrane-Armitage test for binary variables. Differences between categorical variables were assessed using Chi-squared tests.

The association of baseline characteristics with FGF-23 level was assessed using univariate and multivariable linear regression with log transformed FGF-23 as the outcome variable in these models. Resulting beta coefficients were exponentiated, yielding a geometric mean ratio for each independent variable. Percentage difference in the outcome (FGF-23) for each covariate (per standard deviation for continuous variables) was calculated by taking one minus the geometric mean ratio and multiplying by 100. Sex, race, history of CVD, and 25OH vitamin D were forced into the multivariable model due to previously reported associations with FGF-23[14,17,39,40], while selection of the remaining terms was based on a $p<0.1$ in univariate analysis.

Separate linear regression models were used to assess the relationship between both continuous FGF-23 (log base two transformed, due to a skewed distribution, representing the doubling of FGF-23 level) and FGF-23 quartiles of equal size, with the primary outcomes representing memory (Factor 1) and executive function (Factor 2), derived from the principal factor analysis method described above. Three multivariable models were constructed as follows: 1) a parsimonious model was created with adjustment for age, sex and education; 2) an expanded model included additional adjustment for history of CVD and race, which were forced into the model based on previously reported possible associations with FGF-23[13,17], as well as factors that demonstrated differences across quartiles of FGF-23 ($p<0.1$); and 3) a third model additionally adjusted for the mineral metabolism markers calcium, phosphorus and 25OH vitamin D. Secondary analyses repeated the above multivariable analyses for each individual cognitive test. As the Trails B test is a time limited test, a Tobit regression with censoring at 300 seconds was used.[41] As a sensitivity analysis, all models were re-run with FGF-23 as an untransformed, linear term. Analyses were performed using R, version 2.15.1.

ADMA

The association of baseline characteristics with level of ADMA was assessed using univariate and multivariable linear regression. Dialysis vintage and history of cardiovascular disease were forced into the multivariable model while selection of the remaining terms was based on a $p<0.1$ for linear trend across quartiles of ADMA. Linear regression was used to assess the relationship between FGF-23 and the primary outcomes representing memory (Factor 1) and executive function (Factor 2), derived by principal factor analysis. Two multivariable models were constructed as follows: A parsimonious model was created with adjustment for age, sex, education and race. A second model included additional adjustment for history of CVD and vintage as well as factors that demonstrated differences across quartiles of FGF-23 ($p<0.1$).

Results

3.1 FGF-23 results

A total of 263 of 314 patients recruited into the study had stored sample available for measurement of FGF-23. Participants with FGF-23 measured were similar to those without available samples with regards to age, sex, and race/ethnicity, but had shorter dialysis vintage and higher level of education. The mean age of study participants was 63 years, 46% were woman and 22% were African American (Table 1). The mean (SD) FGF-23 level was 5080 RU/ml (5062), with a median of 3098 RU/ml, and inter-quartile range of 1139-7960 RU/ml. Corresponding to higher quartiles of FGF-23, there were higher calcium and phosphorus levels as well as longer dialysis vintage; age, diabetes prevalence, and 25OH vitamin D levels were all significantly lower in the higher FGF-23 quartiles.

In univariate and multivariable analyses younger age, non-diabetic status, higher calcium, higher phosphorus and longer dialysis vintage were all significantly associated with higher FGF-23 levels (Table 2). Calcium and phosphorus were the strongest contributors towards higher FGF-23 level, with a one standard deviation increase resulting in a 46% increase (95% CI: [28, 66]) and 70% increase (95%CI: [49, 94]) in FGF-23 level, respectively.

When adjusted for age, sex, and education level, higher FGF-23 level was associated with worse memory function (representing the change in memory factor for each doubling of FGF-23, (beta = -0.08 SD [95% CI -0.16, -0.01]) but not with executive function (Table 3). FGF-23 was also significantly associated with poorer performance on several individual tests primarily focusing on memory (Short Delay: -0.20 [-0.37, -0.03] and Delayed Recall: -0.17 [-0.34, -0.01] but also on one test of executive functioning (Trails B: 7.29 [0.26, 14.31]). The magnitude of these associations was largely preserved when adjustment was made for possible confounders, including measures of mineral metabolism.

When FGF-23 was analyzed by quartiles, individuals in the highest quartile had worse memory function in comparison with the lowest quartile (-0.42 SD [-0.82, -0.02)). Similarly, the highest quartile was

associated with worse performance on several memory assessments including Immediate Recall Total, Short Delayed Recall, and Delayed Recall (-3.01 [-5.64, -0.39]; -1.32 [-2.44, -0.19] and -1.16 [-2.25, -0.06], respectively) in comparison with the lowest quartile of FGF-23 (Table 4). Significant differences between the highest and lowest quartile were also seen for tests that represent executive functioning processes, including the Digit Symbol-Coding and Trails B tests (-8.68 [-14.76, -2.59] and 48.19 [5.33, 91.06]), respectively. For the component executive function factor, although the highest three quartiles demonstrated worse scores compared to the lowest quartile, no linear trend was seen across quartiles.

Sensitivity Analyses

Results were similar when untransformed, linear FGF-23 was used in multivariable models for both factors and for each individual cognitive test. Similar results were found when PTH was included in multivariable models for each factor.

3.2 ADMA results

257 of 314 patients recruited into the study had stored samples available for ADMA measurement. The mean (SD) ADMA level was 0.77 μmol/L (0.15) (Table 1). Across increasing quartiles of ADMA, there was a lower proportion of black participants, higher proportion of diabetes and history of congestive heart failure, and lower vitamin D 25OH levels.

In both univariate analyses and a multivariable model, female sex, history of CHF and diabetic status were all associated with higher ADMA levels, while black race and higher vitamin D 25OH levels were associated with significantly lower ADMA levels (Table 2).

ADMA was not significantly associated with a lower score for either principal factor (memory or executive function) in both a multivariable model adjusting for age, sex, race, and education status or an extended model adjusting for the above in addition to history of CVD, dialysis vintage, diabetes, history of CHF, serum phosphorus, and vitamin D 25OH (Table 3). For individual component cognitive tests,

higher ADMA levels were associated with lower cognitive performance for the Delayed Recall and Mental Alternation tests in Model 1; this resulted persisted in the extended model for the Delayed Recall test but no for the Mental Alternation test. Although not statistically significant, for both factors and for all cognitive tests, the direction of the beta (mean difference) was consistent with higher ADMA levels and worse cognitive performance.

Discussion

In this cohort of patients treated with maintenance hemodialysis, there was a modest association between higher serum FGF-23 levels and lower cognitive function, after adjustment for several covariates. Specifically, our results showed that higher FGF-23 levels resulted in worse performance in tests assessing memory, findings that remained largely consistent after adjusting for multiple other potential confounders, including those related to mineral metabolism. For the executive function factor and for the Trails B and Digit Symbol-Coding tests, we observed lower levels of cognitive performance when comparing the 2nd through 4th quartiles to the 1st quartile. Additionally, we found several factors which were independently associated with higher FGF-23 levels, including younger age, non-diabetic status, longer dialysis vintage and higher calcium and phosphorus levels.

To our knowledge, there are no previously published studies evaluating the relationship between FGF-23 levels and cognition. Higher FGF-23 levels are associated with multiple adverse outcomes including LVH,[9,10] incident CVD,[13,14] progression of kidney disease[13,16] and mortality in all stages of kidney disease,[12,14-16] although there is debate as to whether FGF-23 is a marker of disease severity/or comorbid conditions or is in the causal pathway leading to these adverse outcomes. In support of the latter, a recent animal study has demonstrated that FGF-23 directly induced LVH, an effect mediated via FGF receptors within cardiac muscle.[18] These same FGF receptors are widely present throughout the brain, with subtypes expressed preferentially in distinct areas of the brain.[19] FGF receptor expression also appears to be altered in conditions of brain injury.[42] It is thus plausible that high levels of FGF-23 may have neurotoxic effects via a pathway independent of markers of mineral metabolism. In support of the latter, adjustment for phosphorus, calcium and 25-OH vitamin D in our models did not diminish the association between FGF-23 and lower cognitive performance. We also note that, although the most consistent association was seen between higher FGF-23 levels and lower function on memory related tests, we cannot be sure whether this translates into FGF having adverse effects on a particular area of the brain, versus there being limited power to detect differences with regard to executive function.

We noted that several patient related factors including younger age, non-diabetic status, longer dialysis vintage, and higher calcium and phosphorus levels were associated with higher FGF-23 levels. In a study of 219 prevalent hemodialysis patients from France, younger age, higher calcium and higher phosphorus levels were associated with higher FGF-23 levels in univariate analysis.[15] In multivariable analysis, only phosphorus remained an independent determinant of FGF-23. This study population differed from ours in several key ways, including a longer dialysis vintage, a lower proportion of diabetic patients, and overall lower mean phosphorus levels, perhaps explaining the difference in findings. FGF-23, which is secreted by bone, is known to have a role within mineral metabolism regulation. Although the exact mechanisms remain unclear, high phosphate intake and high serum calcium are hypothesized to stimulate release of FGF-23,[40,43] which may explain our finding of an association of serum calcium with higher levels of FGF-23. We also saw an association between longer dialysis vintage and higher FGF-23, which may due to the relationship between higher residual renal function and lower FGF-23 levels. A recent study demonstrated that peritoneal dialysis patients with residual kidney function had significantly lower FGF-23 levels that those who were anuric.[44] In a similar fashion, it is likely that patients who have been dialysis dependent for a longer time have lower residual renal function and are therefore more likely to have higher FGF-23 levels. An association between diabetes and lower FGF-23 level was noted in a study of 602 patients during the earlier stages of CKD.[45] Although unconfirmed, it was suggested that decreased bone turnover rates in patients with diabetes compared to non-diabetics may be responsible for lower levels of FGF-23. The association between younger age and higher FGF-23 levels has been reported previously in both ESRD and patients during the earlier stages of CKD.[13,15] The reason for this finding was not discussed in either previous study, but potential explanations include a lower rate of bone turnover in older patients[46,47] (and thereby less FGF-23 secretion), lower bone mass, or lower average phosphorus intake in older patients.[48]

Our study has several limitations which need to be acknowledged when interpreting the study results. First, we did not ascertain residual kidney function and therefore could not adjust for this factor in our

analyses. It has been shown that ESRD patients with higher residual function have lower FGF-23 levels[44] (as they still retain some measure of phosphorus excretion) and may have overall better functional status, which could predispose towards better cognitive function. We did, however, control for dialysis vintage in our analyses, which may serve as a proxy for residual function, partially addressing this limitation. Second, this study is cross-sectional, and therefore we are unable to determine the direction of any observed associations. Third, given the observational nature of the study, unmeasured factors and residual confounding remain possible. Finally, we do not include adjustment for parathyroid hormone (PTH) in our analyses. During the study period the assay used to measure intact PTH was changed, leading us to question the consistency of measured PTH values. Although PTH has been shown to be associated with FGF-23 levels, it has not previously been associated with cognitive function.

Our study also has several strengths. Most importantly, this study represents the first attempt to assess the association between FGF-23 and cognitive performance. Additionally, we administered an array of tests which assess multiple cognitive domains and to address multiple testing associated with our chosen battery of tests, we used principal factor analysis to derive factors which we believe represent memory and executive function. Finally, although our cohort was on average more educated than the average prevalent U.S. hemodialysis patient, it was otherwise similar with regards to age, percent female and prevalence of diabetes, supporting generalizability of our results.

This investigation provides data which suggest that higher FGF-23 levels are associated with poor cognitive performance. Elevated FGF-23 levels may be one of several factors predisposing hemodialysis patients to a high prevalence of cognitive impairment. Future research should attempt to replicate these findings in diverse cohorts of patients with kidney disease, as well as in longitudinal analyses. Finally, further research is required to evaluate the precise mechanism of action by which FGF-23 may affect the brain.

Table 1: Demographics and Clinical Characteristics Stratified by Quartiles of FGF-23

Variable	Full cohort N = 263	Quartile 1 N = 66	Quartile 2 N = 66	Quartile 3 N = 65	Quartile 4 N = 66	p value*
FGF-23 units (RU/ml)	3097 (1139, 7960)	134-1139	1139-3098	3098-7960	7960-15568	NA
Age (years)	63.0 (16.8)	67.1 (17.1)	65.8 (14.2)	62.6 (16.5)	56.6 (17.6)	**<.001**
Female	46%	41%	44%	60%	39%	0.7
Black	22%	18%	23%	18%	30%	0.2
Education						0.5
>2 years College	38%	32%	38%	37%	47%	
High School - 2 years	52%	58%	56%	51%	44%	
< High School	10%	11%	6%	12%	9%	
NAART Verbal IQ	102.6 (12.3)	100.7 (13.1)	104.2 (11.2)	102.4 (11.8)	103.0 (13.2)	0.4
Diabetes	46%	56%	58%	40%	30%	**<.001**
Hypertension	90%	86%	97%	86%	89%	0.9
PVD	22%	29%	21%	14%	24%	0.4
Stroke	17%	11%	21%	14%	23%	0.2
CAD	35%	36%	33%	35%	35%	0.9
CVD	41%	47%	38%	42%	39%	0.5
Cause of ESRD						0.08
Diabetes	33%	47%	38%	28%	20%	
Hypertension	19%	17%	15%	26%	18%	
Unknown	29%	16%	29%	26%	45%	
Glomerulonephritis	19%	20%	18%	20%	17%	
Calcium (mg/dL)	9.0 (0.7)	8.8 (0.7)	9.0 (0.8)	9.1 (0.7)	9.2 (0.7)	**0.002**
Phosphorus (mg/dL)	5.6 (1.5)	4.6 (1.1)	5.3 (1.5)	6.0 (1.1)	6.3 (1.6)	**<.001**
Vitamin D 25OH (ng/ml)	17.7 (7.7)	18.6 (9.7)	18.5 (7.1)	17.0 (6.9)	16.4 (6.7)	0.06
Hematocrit (%)	35.3 (3.6)	35.4 (3.0)	35.3 (3.4)	36.1 (3.5)	34.5 (4.3)	0.3
Albumin (g/dL)	3.8 (0.3)	3.8 (0.3)	3.7 (0.4)	3.9 (0.3)	3.8 (0.4)	0.7
Kt/V	1.51 (0.24)	1.50 (0.21)	1.46 (0.21)	1.60 (0.27)	1.49 (0.25)	0.4
Dialysis Vintage (months)	13.8 (6.4,33.5)	7.5 (4.1,14.5)	11.2 (4.9,18.4)	19.7 (9.7,35.3)	31.3 (13.0,53.7)	**<.001**
DBP (mmHg)	73.0 (12.2)	70.6 (11.6)	72.6 (10.4)	74.5 (11.2)	74.2 (14.9)	0.06
SBP (mmHg)	141.1 (21.0)	141.6 (16.3)	142.7 (20.3)	142.8 (20.1)	137.4 (26.1)	0.3
WBC Count (K/µl)	7.4 (2.4)	7.8 (2.7)	7.2 (2.1)	7.8 (2.6)	7.0 (2.1)	0.2
CRP (mg/L)	5.3 (2.0, 11.4)	5.3 (2.5, 11.2)	6.3 (2.5, 16.6)	3.9 (1.8, 8.7)	5.6 (1.6, 14.7)	0.3
Smoking status						0.3
Current	9%	5%	14%	6%	13%	
Never	39%	36%	31%	40%	49%	
Past	52%	59%	55%	54%	38%	

Presented as mean(SD), %, or median with inter-quartile range as appropriate

*p value for linear trend across quartiles

NAART, North American Adult Reading Test; PVD, peripheral vascular disease; CAD, coronary artery disease; CVD, cardiovascular disease = composite of either CAD or PVD; DBP, monthly average pre dialysis diastolic blood pressure; SBP, monthly average systolic blood pressure; WBC, white blood cell; CRP, c-reactive protein

Complete data was available for all variables, with the exception of CRP for which 9 values were missing

Table 2. Association between Baseline Patient Characteristics and Percent Difference in FGF-23 level

	Unadjusted (N = 263)		Multivariable* (N = 263)	
Variable^	% Difference (95% CI)	p value	% Difference (95% CI)	p value
Age (years)	**-33 (-43,-10)**	**<0.001**	**-15 (-27, -1)**	**0.05**
Female	5 (-22, 43)	0.7	-13 (-37, 13)	0.3
Black	20 (-17, 73)	0.3	0 (-28, 40)	>0.9
Diabetes	**-37 (-54, -15)**	**0.002**	**-18 (-45, -5)**	**0.01**
History of CVD	5 (-30, 30)	0.8	21 (-9, 61)	0.2
Dialysis vintage (years)	**43 (23, 65)**	**<0.001**	**46 (28, 66)**	**<.001**
Diastolic BP (mmHg)	15 (-2, 34)	0.08	-7 (-19, 9)	0.4
Calcium (mg/dL)	**27 (9, 47)**	**0.002**	**46 (28, 66)**	**<.001**
Phosphorus (mg/dL)	**71 (49, 96)**	**<0.001**	**70 (49, 94)**	**<.001**
Vitamin D 25OH (ng/ml)	-11 (-24, 4)	0.14	-7 (-18, 6)	0.3

^All continuous variables have been standardized, the percent difference represents the change per one standard deviation of each relevant covariate

*Adjusted for Age, sex, race, diabetes, history of CVD, dialysis vintage, monthly average diastolic blood pressure, calcium, phosphorus and vitamin

Table 3. Association between doubling of FGF-23 levels and cognitive function

Cognitive Test	sample size	Model 1 Beta (95% CI)	Model 1 p value	Model 2 Beta (95% CI)	Model 2 p value	Model 3 Beta (95% CI)	Model 3 p value
Factor 1 (memory)	243	**-0.06 (-0.12, -0.01)**	**0.02**	**-0.08 (-0.14, -0.01)**	**0.02**	**-0.08 (-0.16, -0.01)**	**0.05**
Factor 2 (executive)	243	-0.04 (-0.10, 0.01)	0.15	-0.02 (-0.08, 0.04)	0.5	-0.03 (-0.10, 0.04)	0.4
MMSE	263	-0.07 (-0.26, 0.11)	0.61	-0.01 (-0.20, 0.19)	0.9	0.09 (-0.14, 0.32)	0.4
Immediate Recall (Total)	261	-0.37 (-0.77, 0.02)	0.06	-0.38 (-0.81, 0.04)	0.08	-0.38 (-0.88, 0.13)	0.14
Short Delayed Recall	260	**-0.20 (-0.37, -0.03)**	**0.02**	**-0.21 (-0.39, -0.02)**	**0.03**	-0.21 (-0.42, 0.01)	0.06
Delayed Recall	259	**-0.17 (-0.34, -0.01)**	**0.05**	-0.17 (-0.35, 0.01)	0.07	-0.15 (-0.36, 0.06)	0.16
Recognition	259	-0.08 (-0.27, 0.12)	0.4	-0.09 (-0.30, 0.11)	0.4	-0.11 (-0.36, 0.13)	0.4
Trails A	244	2.03 (-0.79, 4.85)	0.16	0.53 (-2.50, 3.57)	0.7	0.01 (-3.58, 3.60)	>0.9
Trails B	240	**7.29 (0.26, 14.31)**	**0.04**	7.09 (-0.34, 14.51)	0.06	**7.91 (0.75, 15.08)**	**0.03**
Digit Symbol-Coding	235	-0.47 (-1.43, 0.50)	0.3	-0.31 (-1.31, 0.69)	0.5	-1.05 (-2.23, 0.12)	0.08
Block Design	257	-0.61 (-1.29, 0.06)	0.07	-0.43 (-1.12, 0.25)	0.2	-0.57 (-1.40, 0.24)	0.17
Digits Forward	107	0.10 (-0.16, 0.37)	0.5	0.05 (-0.24, 0.33)	0.7	0.20 (-0.15, 0.55)	0.3
Digits Backward	107	0.15 (-0.10, 0.41)	0.2	0.11 (-0.16, 0.38)	0.4	0.29 (-0.03, 0.61)	0.08
Mental Alternations	107	-0.24 (-1.11, 0.62)	0.6	-0.39 (-1.27, 0.50)	0.4	0.33 (-0.67, 1.34)	0.5
COWAT Animal	108	0.02 (-0.58, 0.61)	>0.9	0.01 (-0.62, 0.65)	>0.9	-0.04 (-0.83, 0.74)	0.9
COWAT Supermarket Items	108	0.09 (-0.61, 0.79)	0.8	-0.01 (-0.74, 0.74)	>0.9	-0.02 (-0.92, 0.89)	>0.9

For each factor, beta represents the change per 1 standard deviation, for cognitive tests beta represents the change in score
For all tests except Trails A & B, a negative value indicates worse performance; for Trails A & B, a positive value indicates worse performance
Model 1 = Adjusted for Age, Sex, and Education Status
Model 2 = Model 1 + Adjustment for Race, Diabetes status, history of CVD, dialysis Vintage, and average pre-HD diastolic blood pressure
Model 3 = Model 2 + Adjustment for calcium, phosphorus, and 25 hydroxy vitamin D
MMSE, Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test

Table 4. Association between Quartiles of FGF-23 and Cognitive Performance*

Cognitive Test	Quartile 1 FGF-23 from 134 to 1139	Quartile 2 FGF-23 from 1139 to 3098 Beta (95% CI)	Quartile 3 FGF-23 from 3098 to 7960 Beta (95% CI)	Quartile 4 FGF-23 from 7960 to 15568 Beta (95% CI)	p value for trend
Factor 1 (memory)	ref	-0.07 (-0.38, 0.25)	-0.17 (-0.53, 0.19)	**-0.42 (-0.82, -0.02)**	**0.04**
Factor 2 (executive)	ref	**-0.29 (-0.57, -0.02)**	**-0.32 (-0.64, -0.01)**	-0.28 (-0.63, 0.07)	0.13
MMSE	ref	-0.37 (-1.26, 0.51)	-0.41 (-1.40, 0.59)	-0.30 (-1.42, 0.82)	0.6
Immediate Recall (Total)	ref	-1.02 (-3.09, 1.06)	-1.89 (-4.25, 0.47)	**-3.01 (-5.64, -0.39)**	**0.02**
Short Delayed Recall	ref	-0.26 (-1.15, 0.62)	-0.30 (-1.30, 0.71)	**-1.32 (-2.44, -0.19)**	**0.03**
Delayed Recall	ref	-0.22 (-1.09, 0.65)	-0.59 (-1.57, 0.39)	**-1.16 (-2.25, -0.06)**	**0.04**
Recognition	ref	-0.18 (-1.15, 0.79)	-0.70 (-1.80, 0.41)	-0.67 (-1.90, 0.56)	0.2
Trails A	ref	7.22 (-6.94, 21.39)	11.78 (-4.33, 27.89)	4.57 (-13.49, 22.63)	0.5
Trails B	ref	33.79 (-0.40, 67.98)	36.05 (-2.44, 74.54)	**48.19 (5.33, 91.06)**	**0.04**
Digit Symbol-Coding	ref	**-5.21 (-10.05, -0.36)**	**-5.59 (-11.02, -0.15)**	**-8.68 (-14.76, -2.59)**	**0.01**
Block Design	ref	-1.46 (-4.69, 1.77)	-2.64 (-6.30, 1.02)	-3.64 (-7.77, 0.48)	0.08
Digits Forward	ref	0.57 (-0.86, 2.00)	0.49 (-1.16, 2.15)	0.31 (-1.43, 2.05)	0.8
Digits Backward	ref	0.53 (-0.82, 1.88)	-0.92 (-2.48, 0.64)	0.42 (-1.22, 2.06)	0.8
Mental Alternations	ref	-2.45 (-6.50, 1.61)	-1.87 (-6.40, 2.67)	-1.72 (-6.56, 3.12)	0.6
COWAT Animals	ref	**-3.44 (-6.72, -0.17)**	-1.01 (-4.73, 2.70)	-1.61 (-5.57, 2.35)	0.7
COWAT Supermarket Items	ref	-1.27 (-5.24, 2.70)	-1.46 (-5.97, 3.05)	-0.04 (-4.84, 4.76)	0.9

Beta represents the mean difference between Quartile 1 and each subsequent quartile. For Factors 1 and 2, this represents a per standard deviation change. For all other tests, this represents the mean difference in score.
For all tests except Trails A & B, a negative value indicates worse performance; for Trails A & B, a positive value indicates worse performance
*Fully adjusted model including age, sex, education level, race, diabetes, history of CVD, dialysis vintage, pre-HD diastolic blood pressure, calcium, phosphorus, and 25 hydroxy vitamin D

Table 5: Cognitive tests used in the neuro-cognitive battery, categorized by the primary cognitive domain evaluated

Function Assessed	Cognitive Test	Scoring	Test Details
Cognitive Screen	Mini-Mental State Exam	Number Correct	Thirty-point questionnaire that samples abilities such as arithmetic, memory, and orientation
Supraspan Learning & Memory	Immediate Recall*	Total initially correct	Assessment of memory in which a list of 12 words is presented during 4 trials, and retention of these words is tested after a delay of 25 to 35 minutes.
	Delayed Recall*	Total number recalled after delay	
	Delayed Recognition*	Number of correctly identified words	
Visual Construction & Fluid Reasoning	Block Design^	Number completed weighted for time	Participants 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
	Digits Span	Total correct number	Participants are asked to repeat lists of numbers read out loud, and to repeat different lists in reverse order.
	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); limit 300 seconds
	Mental Alternations	Total correct number	Participants asked to alternate between sequential numbers and letters by speaking out loud
	COWAT (animals and supermarket items)	Number of correct examples	Participants asked to name as many animals and supermarket items as they can in 1 minute each

* Derived from the Word List Learning subtest of the Wechsler Memory Scale - III (WMS-III)

^From the Weschler adult intelligence scale

Table 6. Principal Factor Analysis Pattern

Primary Cognitive Domain	Test	Percentage of Test Allocated to Each Rotated Factor* Factor 1^	Factor 2^
Memory	Delayed Recall	88%	21%
	Short Delayed Recall	86%	25%
	Immediate Recall Total	75%	35%
	Recognition Total	64%	29%
Both Memory & Executive function	Digit symbol Coding	41%	71%
Executive function	Block Design	26%	64%
	Trails A	10%	75%
	Trails B	37%	71%
Eigenvalues (total variance explained by each factor)		2.87	2.29

An eigenvalue greater than 1.0 is generally accepted to represent adequate loading[49]

**Percentage = Correlation coefficient X 100*

^Based on this loading pattern, Factor 1 was felt to represent Memory and Factor 2 was felt to represent Executive Function

Table 7: Sensitivity Analysis: Association between doubling of FGF-23 and Each Factor, Fully Adjusted Model

Decision rule used	Outcome	Beta (95% CI)	p	# of Observations Removed
Residuals greater than 2/-2 removed	Memory Factor	-0.08 (-0.16, -0.01)	0.03	6 values removed
	Executive Function Factor	-0.07 (-0.13, -0.01)	0.04	5 values removed
Cook's distance greater than 4/n removed	Memory Factor	-0.09 (-0.15, -0.02)	0.02	15 values removed
n = # of observations	Executive Function Factor	-0.07 (-0.13, -0.01)	0.02	14 values removed

Note that the memory factor remains significant with approximately the same beta. The executive function factor becomes significant when either high residual or high leverage points are removed suggesting that several individuals may be driving the null result.

Table 8. Sensitivity Analysis: Association between FGF-23 levels (per increase of 1000 RU/ml) and cognitive function

		Model 1		Model 2		Model 3	
Cognitive Test	sample size	Beta (95% CI)	p value	Beta (95% CI)	p value	Beta (95% CI)	p value
Factor 1 (memory)	243	**-0.03 (-0.05, -0.01)**	**0.02**	**-0.03 (-0.06, -0.01)**	**0.01**	**-0.03 (-0.06, -0.01)**	**0.03**
Factor 2 (executive)	243	-0.01 (-0.02, 0.02)	0.71	0.01 (-0.02, 0.03)	0.63	0.01 (-0.02, 0.03)	0.65
MMSE	263	-0.02 (-0.09, 0.05)	0.61	0.01 (-0.06, 0.08)	0.75	0.04 (-0.04, 0.13)	0.30
Total Recall	261	**-0.15 (-0.29, -0.001)**	**0.05**	-0.15 (-0.31, 0.01)	0.06	-0.14 (-0.32, 0.04)	0.12
Short Delay	260	**-0.09 (-0.15, -0.03)**	**0.01**	**-0.09 (-0.16, -0.02)**	**0.01**	**-0.09 (-0.16, -0.01)**	**0.03**
Delayed Recall	259	**-0.07 (-0.14, -0.01)**	**0.02**	**-0.07 (-0.14, 0.01)**	**0.03**	-0.07 (-0.14, 0.01)	0.08
Recognition	259	-0.02 (-0.09, 0.05)	0.53	-0.02 (-0.10, 0.05)	0.52	-0.03 (-0.11, 0.06)	0.53
Digit Symbol Substitution	235	-0.12 (-0.47, 0.24)	0.53	-0.07 (-0.45, 0.30)	0.69	-0.29 (-0.71, 0.13)	0.18
Blocks Design	257	-0.16 (-0.40, 0.09)	0.21	-0.08 (-0.33, 0.18)	0.56	-0.09 (-0.39, 0.20)	0.53
Digits Forward	107	0.02 (-0.07, 0.11)	0.63	-0.01 (-0.11, 0.08)	0.77	0.02 (-0.09, 0.14)	0.68
Digits Backward	107	0.07 (-0.02, 0.15)	0.11	0.04 (-0.05, 0.13)	0.40	0.10 (-0.01, 0.21)	0.07
Trails A	244	0.20 (-0.82, 1.23)	0.70	-0.41 (-1.52, 0.70)	0.47	-0.75 (-2.00, 0.51)	0.24
Trails B	240	1.56 (-0.99, 4.11)	0.23	1.52 (-1.21, 4.25)	0.27	1.10 (-1.97, 4.18)	0.48
Mental Alternation	107	-0.05 (-0.34, 0.23)	0.72	-0.15 (-0.45, 0.15)	0.32	0.07 (-0.27, 0.41)	0.69
COWAT Animal	108	0.04 (-0.16, 0.24)	0.67	0.04 (-0.18, 0.26)	0.71	0.02 (-0.25, 0.29)	0.87
COWAT Supermarket	108	0.11 (-0.12, 0.33)	0.37	0.07 (-0.18, 0.33)	0.56	0.08 (-0.23, 0.39)	0.60

For each factor, beta represents the change per 1 standard deviation, for cognitive tests beta represents the change in score
For all tests except Trails A & B, a negative value indicates worse performance; for Trails A & B, a positive value indicates worse performance
Model 1 = Adjusted for Age, Sex, and Education Status
Model 2 = Model 1 + Adjustment for Race, Diabetes status, history of CVD, dialysis vintage, and average pre-HD diastolic blood pressure
Model 3 = Model 2 + Adjustment for calcium, phosphorus, and 25 hydroxy vitamin D
MMSE, Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test

Table 9. Association between doubling of FGF-23 and
ıitive Function, Fully Adjusted Model + PTH

	Beta (95% CI)	p value
Factor 1	-0.07 (-0.15, 0.01)	0.08
Factor 2	-0.03 (-0.10, 0.03)	0.3

Table 10. Association between quartile of FGF-23 and Cognitive Function, Fully Adjusted Model + PTH

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value for trend
Factor 1 - memory	reference	-0.04 (-0.35, 0.28)	-0.12 (-0.48, 0.25)	-0.38 (-0.78, 0.02)	.06
Factor 2 - executive	reference	-0.30 (-0.56, -.03)	-0.41 (-.71, -0.10)	-0.32 (-0.66, 0.02)	.06

Table 11. Demographics and Clinical Characteristics of Study Population Stratified by Quartiles of ADMA

Variable	Full Cohort N = 257	Quartile 1 N = 67	Quartile 2 N = 63	Quartile 3 N = 63	Quartile 4 N = 64	p value*
ADMA units (μmol/L)	0.77 (0.15)	0.36-0.66	0.67-0.76	0.77-0.87	0.88-1.27	
Age (years)	63.1 (16.9)	61.6 (16.4)	61.6 (19.0)	62.7 (16.7)	66.6 (15.0)	0.09
Female	46%	37%	44%	51%	52%	0.07
Black	22%	36%	25%	22%	5%	<.001
Education						
>2 years College	38%	39%	46%	35%	31%	0.11
High School to 2 years	52%	55%	37%	56%	59%	
< High School	10%	6%	17%	9%	10%	
NAART	102.4 (12.3)	102.0 (11.8)	101.0 (12.8)	103.4 (11.7)	103.2 (13.1)	0.4
Dialysis vintage (months)	14.0 (6.4:33.5)	14.5 (5.6:36.4)	13.2 (7.1:35.8)	13.4 (7.5: 29.0)	14.0 (5.2:29.7)	0.18
BMI (kg/m^2)	28.4 (7.1)	26.8 (6.2)	29.0 (7.9)	29.0 (7.6)	29.0 (6.3)	0.14
Coronary Artery Disease	35%	33%	37%	32%	39%	0.6
Peripheral Vascular Disease	22%	25%	22%	14%	27%	0.8
Congestive Heart Failure	35%	25%	32%	35%	47%	0.01
Diabetes	47%	40%	38%	54%	55%	0.03
Stroke	16%	7%	19%	25%	14%	0.2
Cardiovascular Disease	41%	40%	40%	38%	47%	0.5
Calcium (mg/dL)	9.0 (0.7)	9.0 (0.8)	8.9 (0.7)	9.0 (0.7)	9.2 (0.7)	0.12
Phosphorus (mg/dL)	5.6 (1.5)	5.2 (1.4)	5.7 (1.8)	5.9 (1.3)	5.6 (1.5)	0.09
Vitamin D 25OH (ng/ml)	17.6 (7.7)	19.8 (9.1)	17.2 (8.1)	16.7 (5.9)	16.7 (6.8)	0.02
Kt/V	1.51 (0.24)	1.54 (0.20)	1.50 (0.25)	1.52 (0.28)	1.49 (0.25)	0.4
Hematocrit (%)	35.3 (3.6)	35.0 (3.8)	35.7 (3.1)	35.1 (4.0)	35.4 (3.7)	0.8
WBC (K/μl)	7.5 (2.4)	7.6 (2.3)	7.3 (2.5)	7.4 (2.4)	7.5 (2.3)	0.8
Albumin (g/dL)	3.8 (0.3)	3.8 (0.3)	3.8 (0.4)	3.8 (0.3)	3.8 (0.3)	0.9
Cause of ESRD						
Diabetes	33%	36%	25%	33%	39%	0.3
Hypertension	19%	18%	18%	24%	17%	
Unknown	10%	27%	38%	33%	21%	
GN	18%	19%	19%	10%	23%	
Smoking status						
Current	10%	8%	13%	11%	7%	0.6
Never	39%	33%	38%	46%	40%	
Past	51%	59%	49%	43%	53%	

Presented as mean(SD), %, or median with inter-quartile range as appropriate

*p value for linear trend across quartiles

NAART, North American Adult Reading Test; Cardiovascular disease = composite of either CAD or PVD; WBC, white blood cell; CRP, c-reactive protein

Table 12. Association of Patient Demographics and Characteristics with ADMA level

Variable	Univariate		Multivariable*	
	Beta (95% CI)	p value	Beta (95% CI)	p value
Age (per 10 years)	0.05 (-0.02, 0.13)	0.16	0.01 (-0.08, 0.09)	0.9
Female	0.30 (0.05, 0.55)	0.02	0.33 (0.08, 0.58)	0.009
Black	-0.63 (-0.92, -0.33)	<0.001	-0.72 (-1.03, -0.41)	<0.001
History of CVD	0.13 (-0.12, 0.39)	0.3	-0.07 (-0.35, 0.21)	0.6
History of CHF	0.35 (0.08, 0.61)	0.01	0.26 (0.01, 0.53)	0.05
Diabetes	0.34 (0.09, 0.59)	0.008	0.29 (0.03, 0.55)	0.03
Phosphorus (per 1 unit increase)	0.07 (-0.02, 0.15)	0.11	0.06 (-0.02, 0.15)	0.12
Vintage (per year)	-0.02 (-0.07, 0.02)	0.3	-0.01 (-0.05, 0.04)	0.9
Vitamin D 25OH (per 10 unit increase)	-0.22 (-0.39, -0.06)	0.008	-0.18 (-0.34, -0.02)	0.03

*Adjusted for all other listed covariates
CVD = cardiovascular disease (composite of either peripheral vascular disease or coronary disease)
CHF = history of congestive heart failure

Table 13. Association between ADMA levels and cognitive performance

Test	Sample size	Model 1 β (95% CI)	Model 1 p value	Model 2 β (95% CI)	Model 2 p value
Factor 1 (memory)	238	-0.08 (-0.19, 0.03)	0.17	-0.09 (-0.21, 0.03)	0.15
Factor 2 (executive)	238	-0.07 (-0.18, 0.03)	0.18	-0.03 (-0.14, 0.08)	0.6
MMSE	257	-0.07 (-0.42, 0.27)	0.7	-0.12 (-0.47, 0.23)	0.5
Immediate Recall (total)	255	-0.18 (-0.92, 0.57)	0.6	-0.11 (-0.89, 0.68)	0.8
Short Delayed Recall	254	-0.26 (-0.57, 0.06)	0.11	-0.24 (-0.57, 0.09)	0.15
Delayed Recall	253	-0.34 (-0.64, -0.03)	0.03	-0.38 (-0.70, -0.06)	0.02
Recognition	253	-0.23 (-0.58, 0.12)	0.2	-0.24 (-0.61, 0.13)	0.2
Digit-Symbol Coding	230	-1.09 (-2.90, 0.72)	0.2	-0.39 (-2.20, 1.42)	0.7
Trails A	239	3.16 (-2.07, 8.39)	0.2	1.50 (-3.86, 6.86)	0.6
Trails B	235	9.21 (-1.05, 19.46)	0.08	6.33 (-4.40, 17.07)	0.3
Block Design	251	-0.64 (-1.82, 0.53)	0.3	-0.66 (-1.88, 0.56)	0.3
Digit Forward	106	-0.36 (-0.87, 0.14)	0.2	-0.21 (-0.75, 0.33)	0.4
Digit Backward	106	-0.29 (-0.78, 0.21)	0.3	-0.09 (-0.61, 0.43)	0.7
Mental Alternations	106	-2.00 (-3.51, -0.48)	0.01	-0.94 (-2.48, 0.61)	0.2
COWAT Animals	107	-0.25 (-1.37, 0.86)	0.7	0.03 (-1.18, 1.25)	0.9
COWAT Supermarket Items	107	-0.97 (-2.22, 0.29)	0.13	-0.88 (-2.24, 0.47)	0.2

Beta represents the mean difference in cognitive score per increase of ADMA by 0.15 μmol/L

For all tests except Trails A & B, a negative value indicates worse performance; for Trails A & B, a positive value indicates worse performance

Model 1: Adjusted for Age, Sex, Education level, and Race
Model 2: Model 1 + Diabetes, History of CHF, History of CVD, Dialysis Vintage, Phosphorus & Vitamin D 25OH

MMSE, Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test

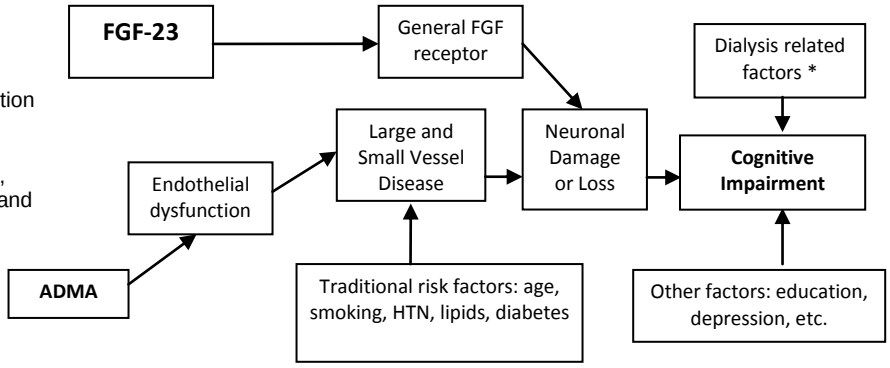
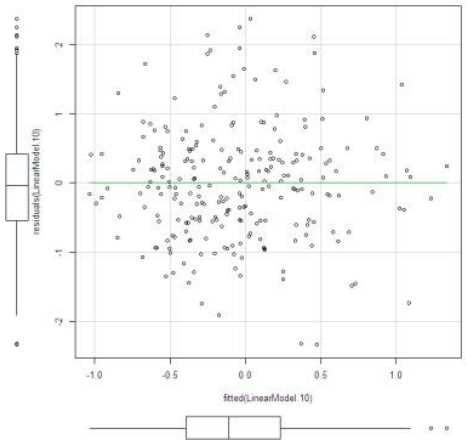


Figure 1: Proposed Mechanisms of Action

* Factors include malnutrition (serum albumin), oxygen delivery (hemoglobin), hemodynamics (BP), clearance (Kt/V), and oxidative stress (homocysteine, CRP)

Figure 2: Model Diagnostics

Residuals v Fitted Values for Factor 1, Final Model



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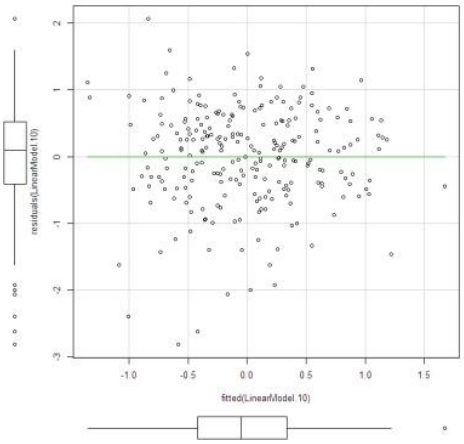
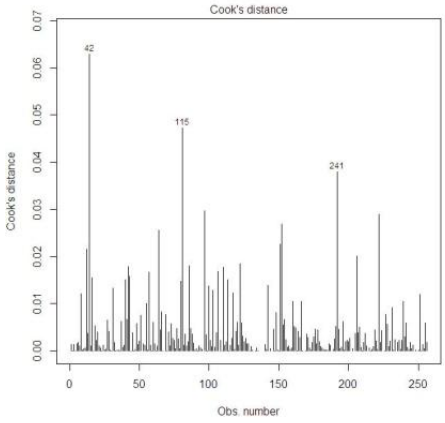


Cook's Distances by Index Number, Factor 1 Final Model



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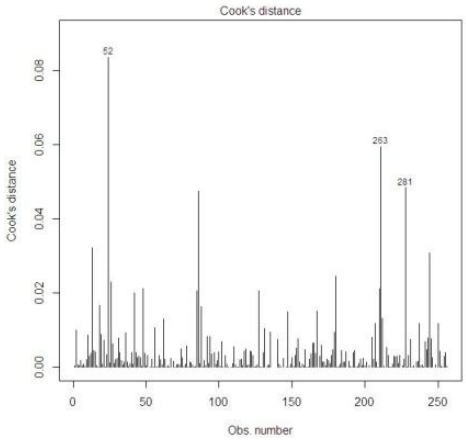
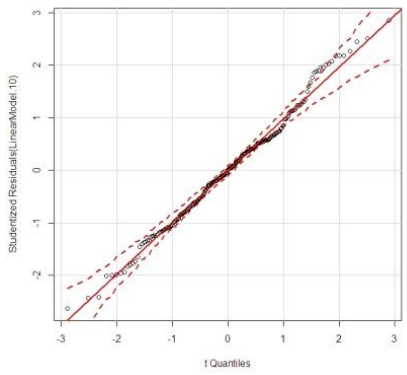


Quantile-Quantile Comparison Plot, Factor 1 Final Model



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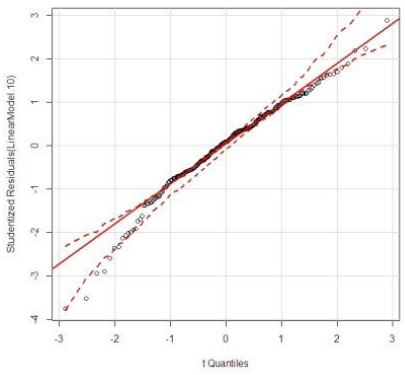
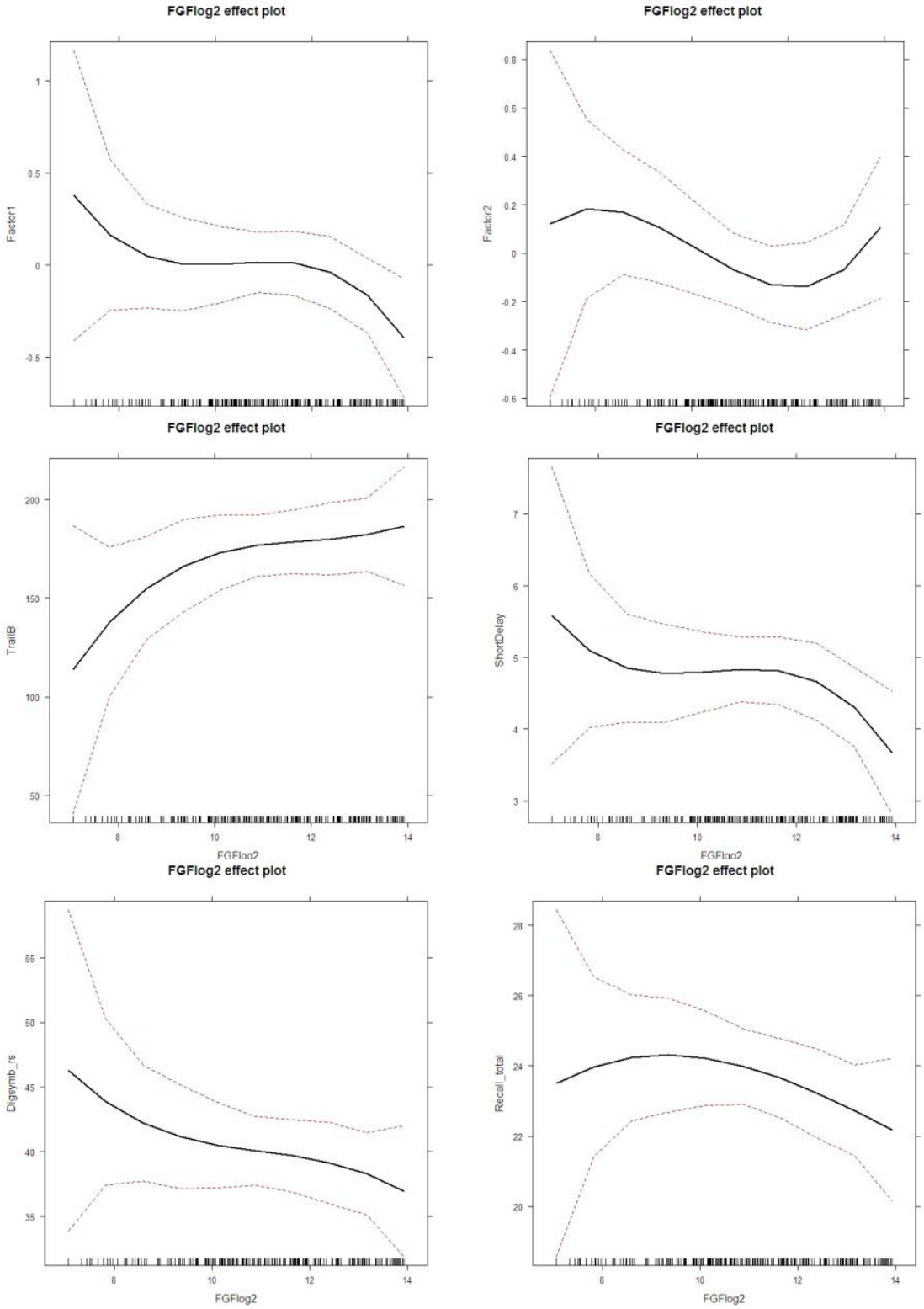


Figure 3: Effect plots All plots used cubic splines with 3 knots to model the log-linear of FGF-23 with cognitive function and were fully adjusted for all previously mentioned covariates. Included are the two primary outcomes (Factor 1 (memory) and Factor 2 (executive function), as well as several individual tests that showed significant associations. Note that for Trails B, a higher score indicates worse performance.



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