**Supplementary Data**

# Table of Contents

| Screening Assessment | |
| --- | --- |
| Montreal Cognitive Assessment (MOCA) | Repeatable and validated tool, used to screen for cognitive impairment. Briefly assesses multiple cognitive domains, with greater sensitivity to vascular cognitive impairment than the mini-mental state exam. Maximal score 30. Score <26 indicative of mild cognitive impairment. |
| **Verbal Fluency** | |
| Phonemic Fluency | Participants are given 1 minute to produce as many unique words beginning with a specific letter, excluding pronouns. Three letters are used, FAS, and score totalled. Deficits in phonemic fluency are more commonly observed in those with deficits in executive function |
| Semantic Fluency | Participants are given 1 minute to produce as many different animals. Animals at different development stages, e.g. lamb and sheep, are only counted once. In contrast to phonemic fluency, deficits in semantic fluency are more commonly observed in those with degenerative disorders such as Alzheimer's' disease. |
| **Executive function** | |
| Trail Making Test A & B (TMTA & TMTB) | Assessment of visual attention and task switching. Participants are asked to connect a set of dots in ascending order as rapidly as possible, whilst maintaining accuracy. TMTA is purely numerical (1-2-3-…) whereas TMTB alternates between letters and numbers (1-A-2-B-3-C-…). The score provided is time taken take to complete; therefore a higher score denotes worse cognitive function. |
| Letter Digit Substitution Test (LDST) | Assessment of processing speed. Participants are allowed one minute to accurately match numbers 1-9 to their randomly allocated paired letter, using a key situated at the top of the page. |
| **Auditory-verbal memory** | |
| Hopkins Verbal Learning Test (HVLT) | Participants are read a list of 12 words and asked to immediately as many as possible. |
| Total Recall | Related to the total number of recalled words after three trials |
| Delayed Recall | Without warning, participants are asked to recall the list following a 20-25 minute delay |
| Retention | Calculated percentage of retained words = delayed recall/highest score from trial 2 or 3 |
| Discrimination Index | Finally, a second list, including the original words, is read. Participants must identify their original words. Discrimination index = number of true positives - number of false positives. |
| **Mood** | |
| Centre for Epidemiologic Studies Depression Scale (CES-D) | Self-ranking depression scale. Higher scores are associated with a greater likelihood of depression. All scoring ≥17 were assessed for core symptoms of depression and, if warranted, onward referral made. |

**Supplementary Table s1** Modified Hachinski protocol of cognitive assessments used both on and off dialysis. All assessments could be competed in less than one hour. For

assessments completed during dialysis all tests were completed within the first 2 hours of dialysis.

|  | MAR | | MCAR | |
| Time versus -15 minutes | Estimate | P-value | Estimate | P-value |
| --- | --- | --- | --- | --- |
| 15 | 0.4072 | 0.4286 | 0.304 | 0.4792 |
| 30 | -0.2094 | 0.6872 | -0.3806 | 0.41 |
| 90 | -1.6049 | 0.0167* | -1.7145 | 0.0063* |
| 180 | -5.7067 | <.0001* | -5.7005 | <.0001* |
| 210 | -5.8809 | <.0001* | -5.8323 | <.0001* |

Note: MAR=missing at random; MCAR=missing completely at random; *$P$<0.05.

**Supplementary Table s2** MAR and MCAR based results for weighted GEE with time as an ordinal variable. MAR ($\beta$=-0.0317, $P$<0.0001) and MCAR ($\beta$ =-0.0313, $P$<0.0001)

based results showed CBFV generally decreased with time as a continuous variable. Each data mechanism provided similar results and parameter estimates for missingness

model show that missing values are likely not related to time ($\beta$ =0.0030, $P$=0.6133) and so MCAR is a reasonable assumption in this case.

| Cognitive Assessment | Correlation with % ΔMFV, Rho | Unadjusted p-value | Rank | FDR adjusted p-value | False detection rate | Bonferroni adjusted p-value significance | Bonferroni |
|---|---|---|---|---|---|---|---|
| HVLT: Retention | 0.046 | 0.70 | 11 | 0.10 | Non-significant | 0.0045 | Non-significant |
| HVLT: Discrimination | -0.057 | 0.63 | 10 | 0.09 | Non-significant | 0.0045 | Non-significant |
| HVLT: Total Recall | -0.089 | 0.45 | 9 | 0.08 | Non-significant | 0.0045 | Non-significant |
| HVLT: Delayed Recall | -0.098 | 0.41 | 8 | 0.07 | Non-significant | 0.0045 | Non-significant |
| CES-D | -0.097 | 0.41 | 7 | 0.06 | Non-significant | 0.0045 | Non-significant |
| LDST | 0.17 | 0.15 | 6 | 0.05 | Non-significant | 0.0045 | Non-significant |
| Semantic | -0.172 | 0.14 | 5 | 0.05 | Non-significant | 0.0045 | Non-significant |
| MOCA | -0.27 | 0.02 | 4 | 0.04 | Significant | 0.0045 | Non-significant |
| Phonemic | -0.302 | 0.01 | 3 | 0.03 | Significant | 0.0045 | Non-significant |
| TMTB | 0.323 | 0.01 | 2 | 0.02 | Significant | 0.0045 | Non-significant |
| TMTA | 0.454 | 0.001 | 1 | 0.009 | Significant | 0.0045 | Significant |

**Supplementary Table s3** Correlation of change in cognitive assessment and MFV as demonstrated inTable 3, with false detection rate and Bonferroni corrections. For comparison, FDR is

calculated using an alpha of 0.1, where each p-value = rank/number of tests multiplied by 0.1.

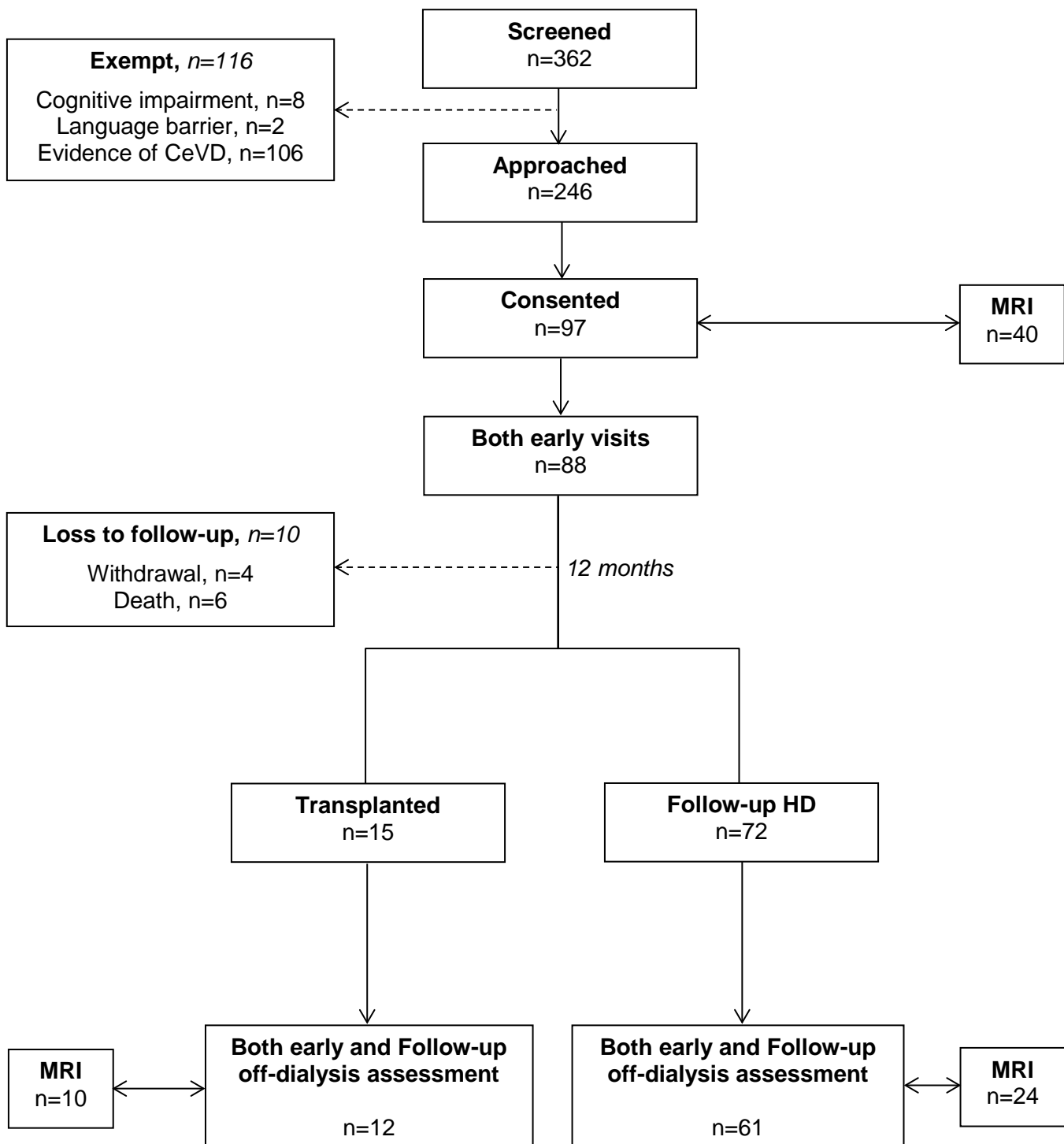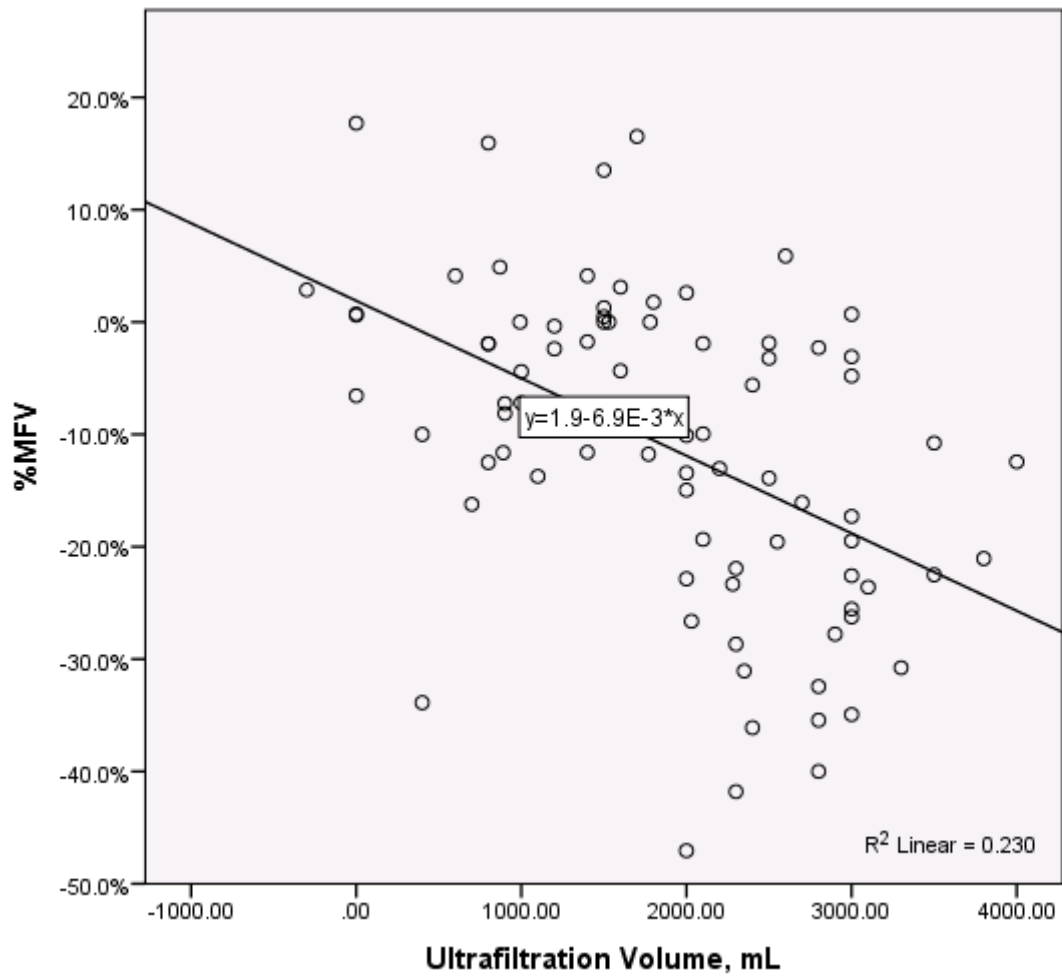| Cognitive Assessment | Correlation with % ΔMFV, Rho | Unadjusted p-value | Rank | FDR adjusted p-value | False detection rate | Bonferroni adjusted p-value significance | Bonferroni |
|---|---|---|---|---|---|---|---|
| **Continued hemodialysis, n= 61** | | | | | | | |
| LDST | -0.085 | 0.55 | 11 | 0.10 | Non-significant | 0.0045 | Non-significant |
| Total Recall | 0.098 | 0.48 | 10 | 0.09 | Non-significant | 0.0045 | Non-significant |
| CES-D | 0.139 | 0.32 | 9 | 0.08 | Non-significant | 0.0045 | Non-significant |
| Discrimination | 0.149 | 0.30 | 8 | 0.07 | Non-significant | 0.0045 | Non-significant |
| Phonemic | 0.15 | 0.28 | 7 | 0.06 | Non-significant | 0.0045 | Non-phognificant |
| TMTA | -0.209 | 0.15 | 6 | 0.05 | Non-significant | 0.0045 | Non-significant |
| Retention | 0.219 | 0.15 | 5 | 0.05 | Non-significant | 0.0045 | Non-significant |
| Semantic | 0.201 | 0.15 | 4 | 0.04 | Non-significant | 0.0045 | Non-significant |
| Delayed Recall | 0.243 | 0.08 | 3 | 0.03 | Non-significant | 0.0045 | Non-significant |
| MOCA | 0.276 | 0.04 | 2 | 0.02 | Non-significant | 0.0045 | Non-significant |
| TMTB | -0.403 | 0.005 | 1 | 0.009 | Significant | 0.0045 | Non-significant |
| **Transpalnted at follow-up, n=12** | | | | | | | |
| MOCA | 0.086 | 0.81 | 11 | 0.10 | Non-significant | 0.0045 | Non-significant |
| Delayed Recall | -0.123 | 0.75 | 10 | 0.09 | Non-significant | 0.0045 | Non-significant |
| Discrimination | 0.273 | 0.45 | 9 | 0.08 | Non-significant | 0.0045 | Non-phignificant |
| TMTB | -0.317 | 0.41 | 8 | 0.07 | Non-significant | 0.0045 | Non-signifcant |
| Total Recall | 0.329 | 0.35 | 7 | 0.06 | Non-significant | 0.0045 | Non-phognificant |
| CES-D | -0.334 | 0.35 | 6 | 0.05 | Non-significant | 0.0045 | Non-significant |
| Retention | -0.358 | 0.31 | 5 | 0.05 | Non-significant | 0.0045 | Non-significant |
| LDST | 0.383 | 0.28 | 4 | 0.04 | Non-significant | 0.0045 | Non-significant |
| TMTA | -0.5 | 0.17 | 3 | 0.03 | Non-significant | 0.0045 | Non-significant |
| Semantic | 0.609 | 0.06 | 2 | 0.02 | Non-significant | 0.0045 | Non-significant |
| Phonemic | 0.758 | 0.01 | 1 | 0.009 | Non-significant | 0.0045 | Non-significant |

**Supplementary Table s4** Correlation of change in cognitive assessment and MFV as demonstrated inTable 4, with false detection rate and Bonferroni corrections. For comparison, FDR is

calculated using an alpha of 0.1, where each p-value = rank/number of tests multiplied by 0.1.

| | Continued Hemodialysis, n=72 | Transplanted during study, n=15 | p-value |
|---|---|---|---|
| Median Age [IQR] | 60 [52,67] | 51 [40,63] | 0.02 |
| Female, n [%] | 34 [41.5] | 6 [40] | 0.92 |
| Ethnicity, n [%] | | | |
| European | 80 [97.6] | 13 [86.7] | 0.05 |
| Asian | 2 [2.4] | 2 [13.3] | |
| Primary Renal Diagnosis, n [%] | 16 [19.5] | 2 [13.3] | |
| Diabetes | 20 [24.4] | 0 | |
| Glomerulonephritis | 16 [19.5] | 4 [26.7] | |
| Interstitial | 16 [19.5] | 4 [26.7] | |
| Multisystem | 14 [17.1] | 5 [33.3] | 0.18 |
| Other | | | |
| Past Medical History, n [%] | | | |
| Hypertension | 74 [90.2] | 11 [73.3] | 0.07 |
| Diabetes mellitus | 26 [35.4] | 3 [20] | 0.25 |
| Ischemic heart disease | 19 [23.2] | 2 [13.3] | 0.40 |
| Congestive cardiac | 11 [13.4] | 0 | 0.13 |
| failure | 7 [8.5] | 0 | 0.24 |
| Peripheral Vascular | 11 [13.4] | 0 | 0.13 |
| disease | 17 [20.7] | 4 [26.7] | 0.61 |
| Atrial Fibrillation | | | |
| Depression | | | |
| Duration of ESRD, median years [IQR] | 2.09 [0.73,4.54] | 0.6 [0.22,1.61] | <0.01 |
| Dialysis Related Variables, median [IQR] | | | |
| Pre-SBP | 143.4 [121.3,158.5] | 142.5 [121.0,157.5] | 0.85 |
| Pre-DBP | 72.3 [65.0,79.8] | 78.5 [70.8,84.7] | 0.08 |
| Post-SBP | 129.6 [112.7,148.3] | 130.8 [121.8,135.7] | 0.94 |
| Post-DBP | 68.4 [59.5,76.2] | 73.7 [61,88.3] | 0.15 |
| UF Volume | 2.07 [1.5,2.5] | 1.73 [1.28,2.49] | 0.34 |
| Dialysis Access, n [%] | | | |
| AV access | **59** [72] | 10 [66.7] | |
| Central Venous Catheter | **23** [28] | 5 [33.3] | 0.68 |
| Laboratory Values, median [IQR] | | | |
| Serum Adjusted Calcium | 2.39 [2.28,2.46] | 2.34 [2.25,2.56] | 0.89 |
| Serum Phosphate | 1.7 [1.47,2.01] | 1.94 [1.71,2.05] | 0.10 |
| Hemoglobin | 112.5 [102,122] | 113.3 [96.7,118.7] | 0.82 |
| Serum Albumin | 32.7 [30,35] | 33.7 [31.7,35.0] | 0.49 |
| PTH | 55.9 [36.4,92.5] | 85.7 [59.1,156.7] | 0.02 |
| Urea Reduction Ratio | 72.8 [70,77.5] | 73.0 [68,78] | 0.95 |
| Years of Education, median [IQR] | 12 [11,14] | 13 [11,14] | 0.61 |

**Supplementary Table s5** Demographic of study cohort, split by those who remains on dialysis, or were transplanted. Abbreviations: ESRD, end-stage renal disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; UF, utrafiltration; AV, ateriovenous; PTH, parathyroid hormone.

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                                     ┌─────────────────────┐
                                     │     Screened        │
                                     │      n=362          │
                                     └─────────────────────┘
┌──────────────────────────────┐                │
│ Exempt, n=116                │                │
│                              │ ◄------------  ▼
│ Cognitive impairment, n=8    │     ┌─────────────────────┐
│ Language barrier, n=2        │     │     Approached      │
│ Evidence of CeVD, n=106      │     │      n=246          │
└──────────────────────────────┘    └─────────────────────┘
                                                │
                                                ▼
                                     ┌─────────────────────┐        ┌──────────┐
                                     │     Consented       │◄──────►│   MRI    │
                                     │      n=97           │        │   n=40   │
                                     └─────────────────────┘        └──────────┘
                                                │
                                                ▼
                                     ┌─────────────────────┐
                                     │  Both early visits  │
                                     │      n=88           │
                                     └─────────────────────┘
┌──────────────────────────────┐                │
│ Loss to follow-up, n=10      │                │
│                              │ ◄----------- 12 months
│ Withdrawal, n=4              │                │
│ Death, n=6                   │                │
└──────────────────────────────┘                │
                                    ┌───────────┴───────────┐
                                    ▼                       ▼
                          ┌──────────────────┐   ┌──────────────────┐
                          │   Transplanted   │   │   Follow-up HD   │
                          │      n=15        │   │      n=72        │
                          └──────────────────┘   └──────────────────┘
                                    │                       │
                                    ▼                       ▼
┌────────┐      ┌──────────────────────────┐  ┌──────────────────────────┐      ┌────────┐
│  MRI   │◄────►│ Both early and Follow-up │  │ Both early and Follow-up │◄────►│  MRI   │
│  n=10  │      │ off-dialysis assessment  │  │ off-dialysis assessment  │      │  n=24  │
└────────┘      │                          │  │                          │      └────────┘
                │          n=12            │  │          n=61            │
                └──────────────────────────┘  └──────────────────────────┘
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**Supplementary Figure s1** Flow chart demonstrating recruitment, follow-up and participant attendance to study visits and MRI. Abbreviations: CeVD, Cerebrovascular disease; MRI, Magnetic Resonance Imaging; HD, Hemodialysis

The plot shows a scatter of data points with the regression line labeled $y = 1.9 - 6.9E{-}3*x$ and $R^2 \text{ Linear} = 0.230$. The x-axis is "Ultrafiltration Volume, mL" ranging from -1000.00 to 4000.00, and the y-axis is "%MFV" ranging from -50.0% to 20.0%.

**Supplementary Figure 2** Correlation plot of UF and % decline MFV, Spearman's rho -0.512, p<0.001.

More positive ultrafiltration volumes correlate with more negative %decline in MFV.
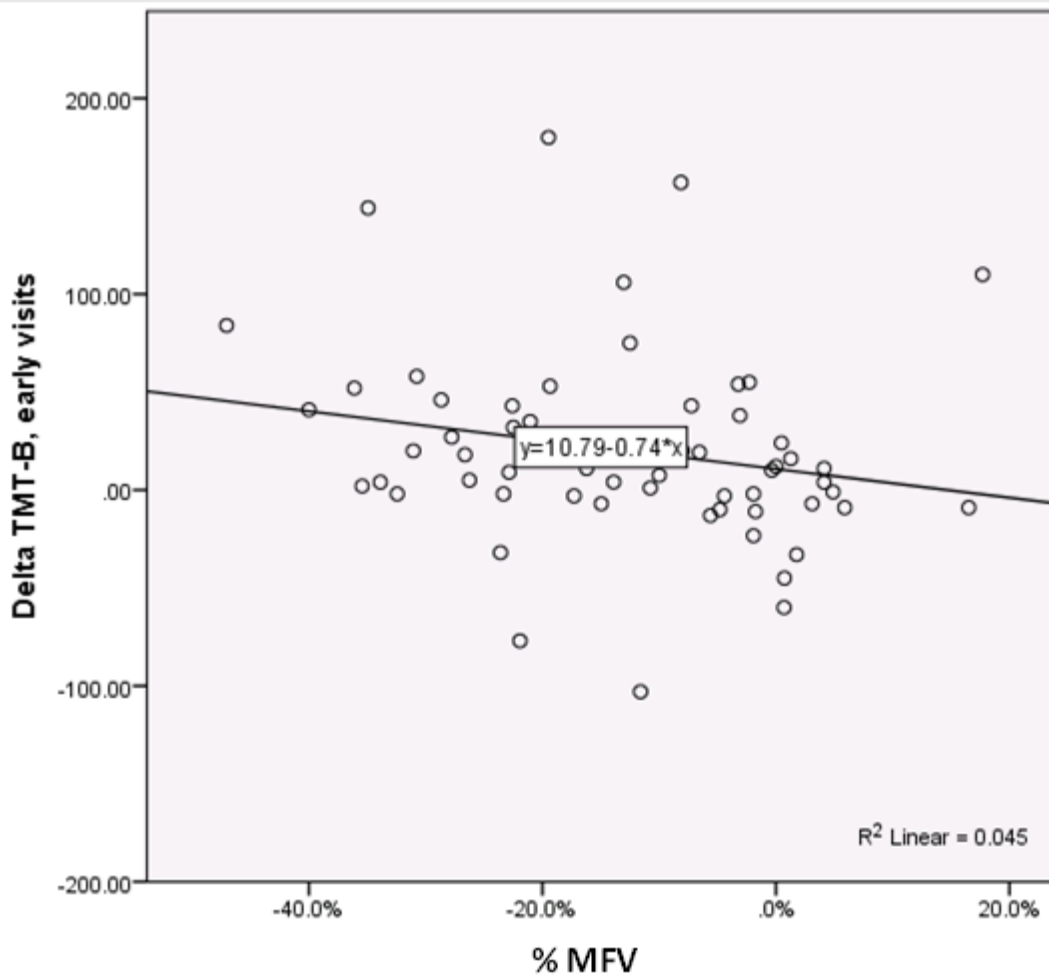
**Supplementary Figure 3** Correlation plot of delta TMT-B (early visits) and % decline MFV -

Spearman's rho -0.323, p=0.01. Delta score is calculated as score during dialysis minus score off

dialysis. Thus, for TMT-B, if time taken to complete on dialysis is longer then the delta score is

positive. A more positive delta TMT-B denotes worsening of executive function during dialysis.
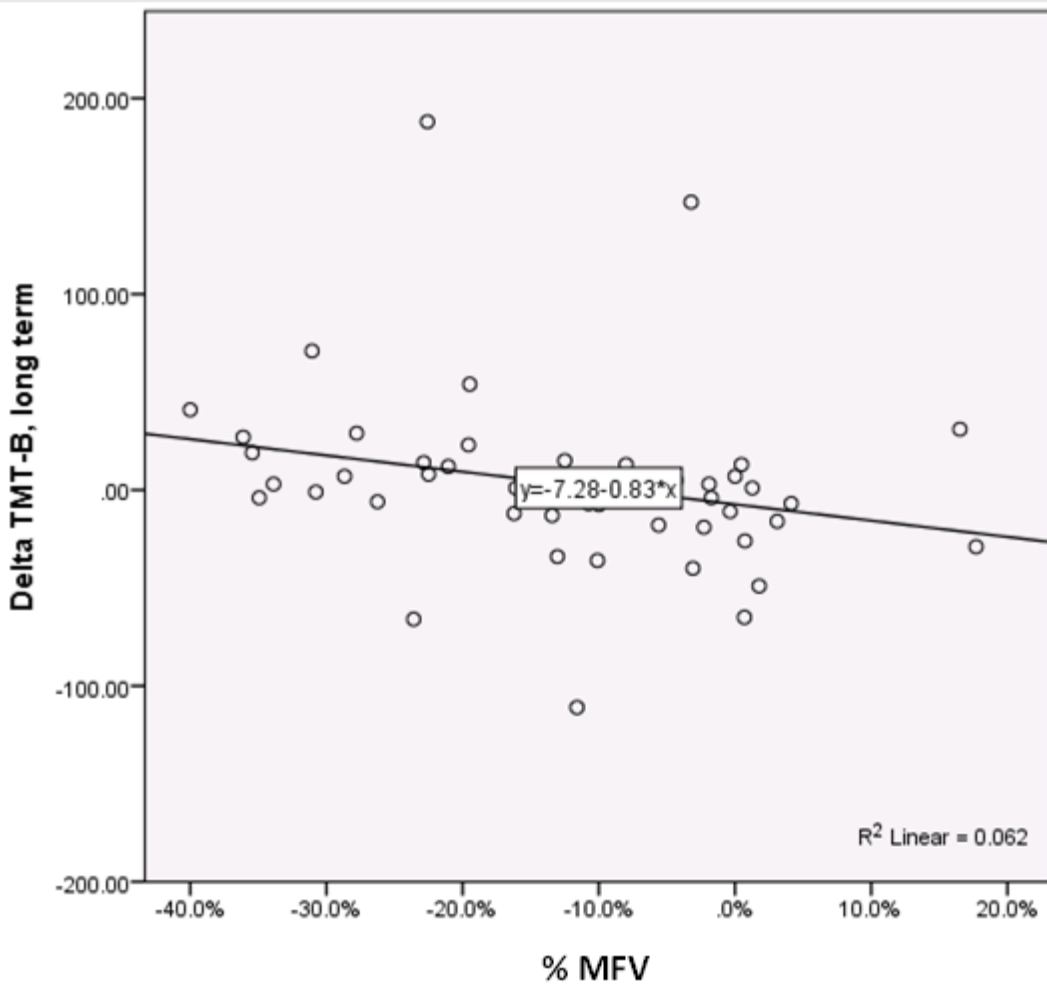
**Supplementary Figure 4** Correlation plot of delta TMT-B (long term) and % decline MFV in those on continued HD - Spearman's rho -403, p=0.005. Delta score is calculated as score at follow-up minus score at baseline. Thus, for TMT-B, if time taken to complete is longer at follow-up delta score is more positive. A more positive delta TMT-B denotes a worsening executive function at follow-up.

The plot shows a scatter plot with the x-axis labeled "Delta WMH Volume, mL" ranging from -2.00 to 4.00, and the y-axis labeled "Delta CES-D, long term" ranging from -30.00 to 20.00. A regression line is shown with the equation y=-2.12+3.34*x. The text "R² Linear = 0.297" appears in the lower right.
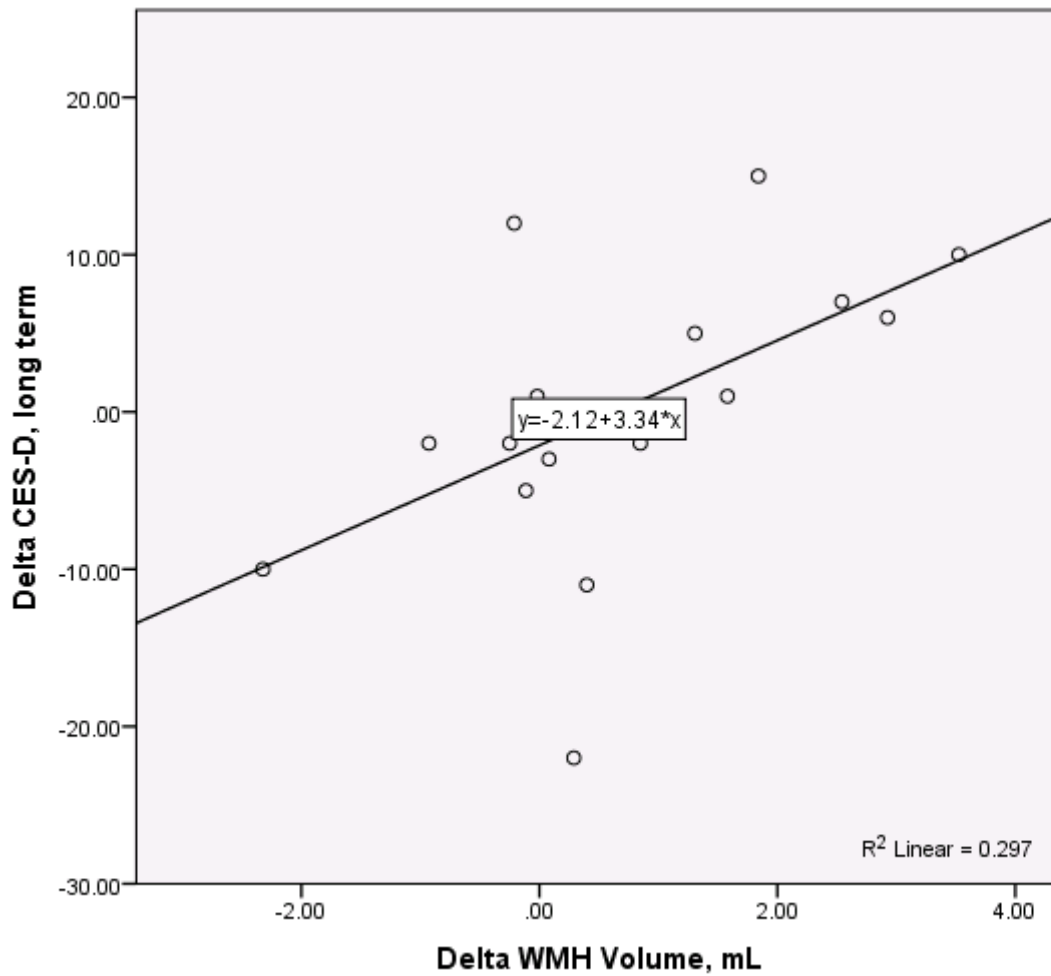
**Supplementary Figure 5** Correlation plot of delta CES-D (long term) and delta WMH volume in those on continued HD - Spearman's rho 485, p=0.03. Delta score is calculated as score at follow-up minus score at baseline. Thus, for CES-D, if depression scoring is greater at follow-up delta score is more positive. A more positive delta CES-D denotes a worsening in depressive symptoms at follow-up.
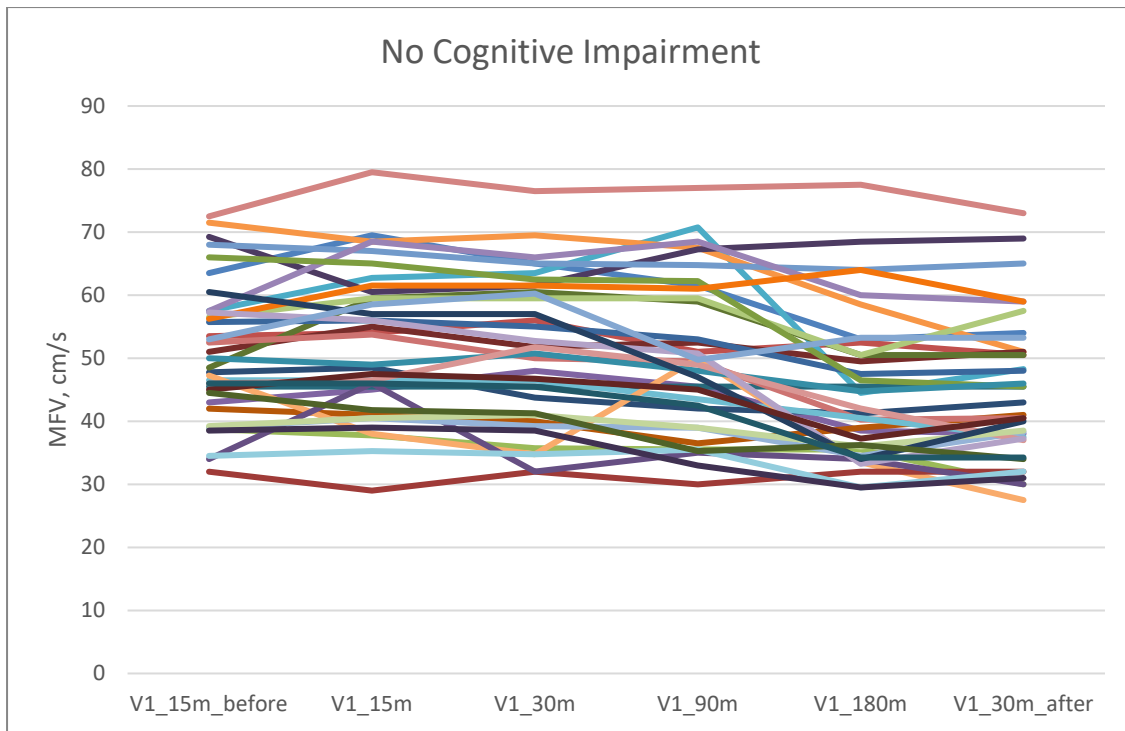
**Supplementary Figure 6** Trajectory of MFV during dialysis, in those without cognitive impairment
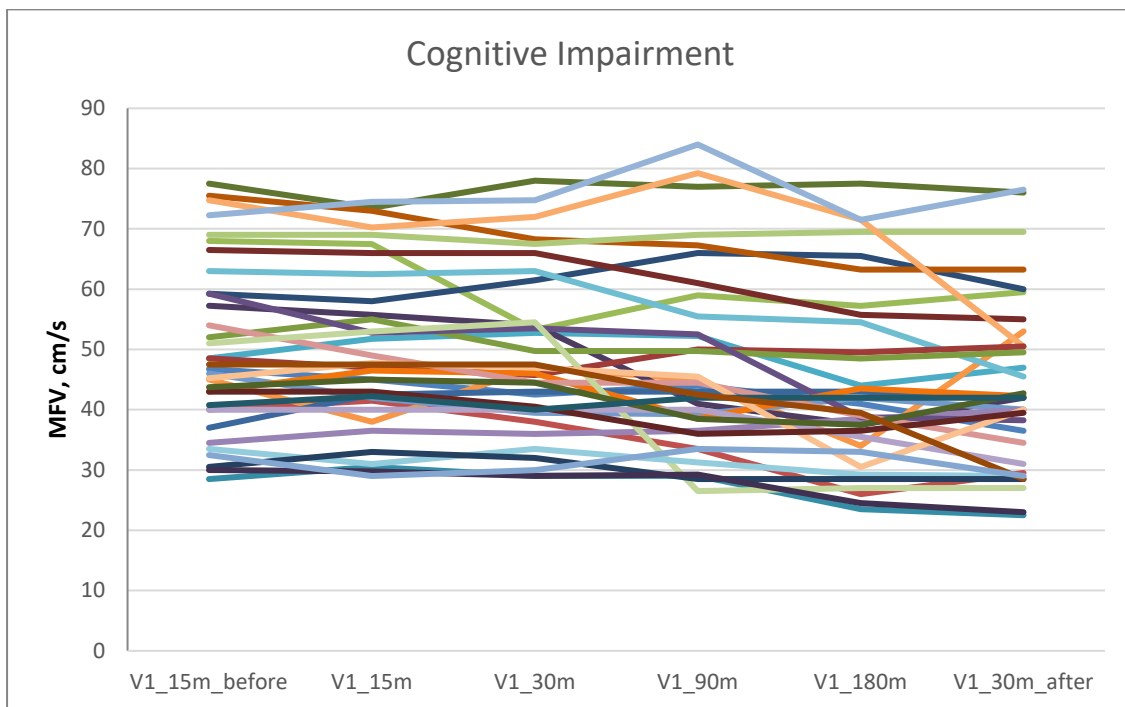


**Supplementary Figure 7** Trajectory of MFV during dialysis, in those with cognitive impairment
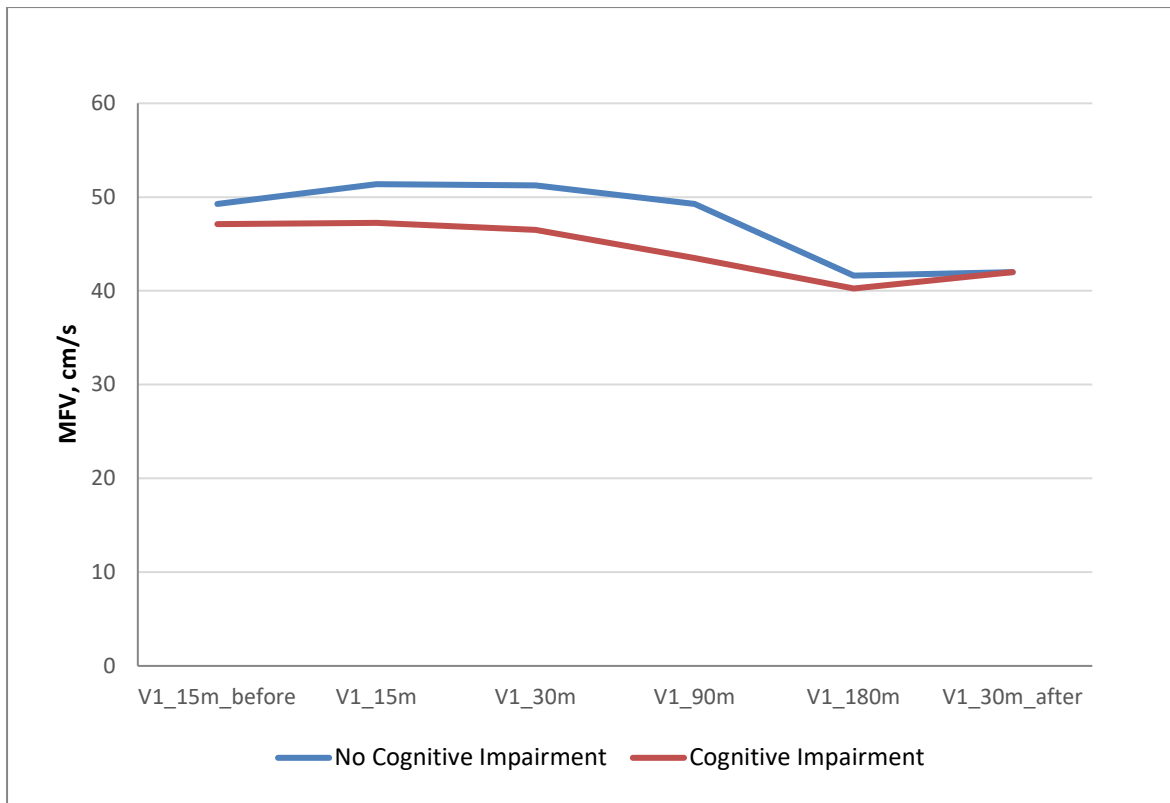
**Supplementary Figure 8** Trajectory of MFV during dialysis, in those with and without cognitive impairment grouped