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Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients

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Significance Statement (119 words)

Recent data suggest hemodialysis is capable of reducing cerebral blood flow. The reported propensity of dialysis related cognitive impairment to present as executive dysfunction has led many to assume alterations in cerebral circulation are implicated in cognitive decline, yet this observation has not been formally tested. This prospective observational study uses real time vascular imaging, brain MRI and neurocognitive assessments to demonstrate a correlation between dialysis related decrease in cerebral blood flow and tests of executive function during a single dialysis session and following 12 months of ongoing treatment. MRI demonstrates progressive markers of small vessel disease in those on dialysis, and an increase in anisotropic diffusion following transplant. These observations underpin one mechanism of cerebral injury in hemodialysis.

Abstract

Background:

The immediate and longer-term effects of hemodialysis on the cerebral circulation, structure and function are poorly understood.

Methods:

Prospective observational cohort study of adults receiving chronic hemodialysis. Cerebral arterial mean flow velocity (MFV) throughout dialysis was assessed by transcranial Doppler ultrasound. Cognitive function was assessed during and out-with dialysis and again at 12months. Brain magnetic resonance imaging (MRI) was performed to assess atrophy, white matter hyperintensities (WMH) and diffusion parameters. Correlations between MFV, cognitive scores and changes on MR were tested.

Results:

97 patients, median age [IQR] 59 [51, 67] years were recruited. MFV declined during dialysis (47.38–40.75cm/s, $p<0.001$), correlating with ultra-filtrate volume ($R=0.512$, $p<0.001$). %Decline in MFV (median [IQR] -10[-21.9, 0.0] %) correlated with intradialytic decline in cognitive function: namely global function ($R=0.270$, $p=0.02$); Trail-Making-Test (TMT) A ($R=-0.454$, $p<0.001$); TMT-B ($R=-0.323$, $p=0.01$ and verbal fluency ($R=0.302$, $p=0.01$). At follow-up, 73 patients were available for repeat testing, 34 underwent repeat MRI. 15 patients were transplanted during follow-up. Following 12 months of continued dialysis, n=61, %decline in MFV correlated with lower global and executive function ($R=0.276$, $p=0.043$ and $R=-0.403$, $p=0.005$) and WMH burden progressed (3.36 vs 2.96 ml, $p=0.018$). Following

transplantation, memory improved (delayed recall 9.5 vs 6.5, p=0.02). Fractional anisotropy of white matter (0.29 vs 0.28, p=0.016) increased, correlating with improving executive function (R=-0.886, p=0.019).

Conclusions:

Hemodialysis induces transient decline in cerebral blood flow, correlating with intradialytic cognitive dysfunction. Progressive cerebrovascular disease occurs in those continuing dialysis. Improved cognitive function and cerebral diffusion is observed following transplantation.

Introduction

Cognitive impairment is highly prevalent in those on hemodialysis (HD); up to 70% in an unselected cohort demonstrated cognitive impairment[1]. The aetiology of cognitive impairment in HD is multifactorial: dialysis is associated with profound metabolic abnormalities, chronic inflammation and oxidative and hemodynamic stressors. However, two important findings support the theory that cerebrovascular disease is the primary driving force. Specifically, dialysis preferentially induces deficits in executive function[2–4], a pattern traditionally observed early in vascular cognitive impairment but only a later complication of other dementias such as Alzheimer's disease[5] and that more regular frequent dialysis does not improve cognitive function[6], whereas renal transplantation can[7].

The frequency of cerebrovascular disease in people with end-stage renal disease (ESRD) is up to 10-fold greater[8] compared to the general population and mortality rates approximately three-fold greater[9]. Although conventional stroke risk factors such as hypertension are ubiquitous in ESRD and partly responsible, it is likely renal specific factors contribute to this inordinate difference. For example, there is increasing evidence that both initiation[10] of and exposure[11,12] to HD for ESRD is associated with stroke, although the mechanism is not fully explained. Interestingly, this risk appears to be reduced by receiving a renal transplant[13].

The concept that HD can induce cerebral injury is supported by previous studies. Two recent prospective European studies have demonstrated evidence of decreased intradialytic cerebral perfusion[14,15], relating this to dialysis related factors such as intradialytic hypotension or ultrafiltration volume. Alterations in cerebral structure are also described. For example, white matter hyperintensities (WMH), a marker of small

vessel disease, are present incidentally in 11-21% of the general population aged around 64 years[16] whereas this rises to 52% in those on HD[17]. Increasing WMH burden is associated not only with stroke[18] but also cognitive impairment[1].

Real-time non-invasive measurement of cerebral blood flow is possible using transcranial Doppler (TCD) ultrasound, a non-invasive, inexpensive tool which is well tolerated and capable of performing repeated measurement throughout a dialysis session. Our primary hypothesis is that cerebral blood flow, measured by TCD, is reduced by hemodialysis and correlates with a decline in intradialytic cognitive function. Secondarily, we hypothesize that a reduction in cerebral blood flow is capable of reducing longer term cognitive function, inducing ischemic damage as measured by white matter hyper-intensity (WMH) burden and that progressive ischemia on brain MRI at 12 months will correlate with progressive cognitive decline.

Therefore, we present a prospective investigation of real-time dialysis related cerebral blood flow, cognitive function on and off dialysis and brain MRI findings over a 12-month follow-up of continuous treatment for ESRD.

The primary aim of this study was to explore whether HD was associated with changes in cerebral blood flow and determine whether these changes relate to intra-dialytic cognitive dysfunction. Our secondary aims focus on (1) assessment of longitudinal changes in cerebral structure and function using brain MR imaging and cognitive assessment at baseline and after 12 months, correlating this to alterations in cerebral blood flow and (2) to compare cognitive outcomes at follow-up in those who remain on hemodialysis and those who receive a renal transplant.

Methods

Recruitment began in April 2015 and the first visit took place on 3 June 2015. All visits were completed by 7 July 2017. Participants were asked to attend three visits over a 12 month follow-up period. Two visits took place within the first month: one during their routine dialysis treatment (intra-dialytic assessment), and a second on a non-dialysis day (inter-dialytic assessment). At 12 months a repeat non-dialysis assessment was performed.

Study participants

All adult patients aged 18-85 inclusive receiving hospital hemodialysis for ESRD at the Glasgow Renal and Transplant unit were considered. We approached all adults who were expected to remain on hospital hemodialysis for ≥ 6months. Exclusion criteria were: inability to consent, poor comprehension of English language, a prior diagnosis or neuroimaging evidence of cerebrovascular disease and prior diagnoses of cognitive impairment. Neuroimaging evidence of cerebrovascular disease included all those with prior ischemic or hemorrhagic stroke in addition to those with evidence of small vessel disease. Written informed consent was completed for each participant. This study was approved following ethical review by the West of Scotland research ethics committee 5, reference REC 15/WS/0024 and registered on ClinicalTrials.gov under identifier NCT02393222.

Clinical Variables

Patient demographics were acquired from the electronic patient record. Duration of ESRD was calculated in years from date of first RRT commencement until date of first visit. Pre- and post-blood pressure and ultrafiltration volumes were recorded and

presented as an average of the last 6 readings. Laboratory values utilised the three latest results preceding their first visit. During the intradialytic assessment visit, blood pressure and weight were recorded before and after dialysis, and UF rate calculated as volume of fluid removed divided by duration of session.

Dialysis Schedule

This observational study was designed to assess the effect of dialysis in a 'real-world' cohort, without intervention or interference with each participant's routine treatment schedule. All participants underwent their routine prescribed dialysis treatment. The median [IQR] duration of dialysis was 4 [4, 4.5] hours, with median [IQR] blood flow rates of 300 [287.5, 305.0] mL/min. Dialysate temperature throughout all units is set at 36.5^{o}C. The first dialysis session following the 'long gap' was completely avoided. All Doppler readings were performed with patients sitting upright. It was essential that patients remained comfortable during their cognitive assessments, therefore food and rest periods were permitted.

Cognitive Assessments

Assessments were carried out by medical and nursing staff following training in appropriate use of the assessments by an experienced psychologist. At the mid-point of our study, re-training was performed to ensure consistency of assessment. Intra-dialytic testing was performed within the first 2 hours of dialysis, omitting the first 15 minutes for initial physiological monitoring and routine nursing checks. All physical assessment as part of routine dialysis was performed manually, by usual dialysis nursing staff. The dialysis unit staff were aware to keep interruption to a minimum and cognitive testing was halted during scheduled blood pressure checks.

Where practically possible, in order to account for environmental effects on cognitive function participants returned to the dialysis unit for their inter-dialytic assessment.

A modified 30-minute National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) neuropsychological battery was used to assess cognitive function. This well-validated protocol was chosen due to its feasibility, acceptability and increased sensitivity at detecting vascular cognitive impairment. It consists of verbal and written assessments of multiple cognitive domains. Specifically, we included the Montreal Cognitive Assessment, using the accepted cut-off of <26 to define cognitive impairment. Verbal fluency was assessed using phonemic and semantic fluency, executive function using Trail-Making tests A & B (TMTA, TMTB) and the letter-digit substitution test (LDST) and auditory-verbal memory via the Hopkins Verbal Learning Test (HVLT). Finally, an assessment of mood was performed using the Centre for Epidemiologic Studies Depression Scale. Further information on each assessment is described in supplementary table s1. The MOCA was used to quantify 'cognitive impairment', therefore presented as an education adjusted score (addition of 1 for those with 12 year or less education). All other scores are presented as raw, unadjusted data.

In an attempt to blunt possible learning effects, all visits were held a minimal 14 days apart. Further, we used versions 7.1, 7.2 and 7.3 of the MOCA and HVLT 1, 2, 5 and 6 at differing visits throughout the study.

In cases where writing was not possible, for example a participant's inability or unwillingness to move their dominant arm during dialysis (n=9), the MOCA-BLIND method was used – adjusting the cut-off for cognitive impairment <18, and the verbal LDST was performed.

Imaging

Following training from a research neuro-sonographer, all transcranial Doppler ultrasound was performed by one operator (MDF). Bilateral insonation of the middle cerebral arteries via trans-temporal windows was attempted in all patients during their intra-dialytic visits using the ST3 Transcranial Doppler Spencer Technologies TCD (Redmond, WA, USA) with Power M-Mode 150. Measurements were performed with a sample of 6–9 mm and 2-MHz probes held in situ using a Marc600 head frame. Participants were asked to wear this throughout their dialysis session. Power began at 100mW/cm^{2}power and was reduced to the lowest possible setting for patient comfort. TCD recordings started at 50mm of depth and adjusted to achieve the clearest possible signal. In participants with bilateral temporal windows, a median value was calculated for analyses. Recording were taken approximately 15 minutes prior to commencing dialysis, at set time intervals throughout dialysis and within 30 minutes of completion (figure 1). Change in MFV was calculated as the reading at 30 minutes after completion minus the reading 15 minutes prior to commencing of dialysis.

Brain magnetic resonance imaging (MRI) was performed in a subset of patients using 3-T MRI Siemens research scanners (MAGNETOM Verio or PRISMA, Siemens Healthcare, Erlangen, Germany); allocated randomly as the first 40 consented to the study willing and with no contraindications to MRI. All follow-up imaging was performed on their original scanner to allow direct comparison. T1, T2, Fluid Attenuated Inversion Recovery (FLAIR) and Diffusion Tensor Imaging (DTI) sequences were used to determine markers of atrophy (determined by change in volume of cortical grey matter, normal appearing white matter and supratentorial

CSF volumes), white matter hyperintensity burden and cerebral diffusion, calculated as mean diffusivity (MD) and fractional anisotropy (FA).

Image analyses

MR images were analysed using volumetric analyses software. The first step in automated extraction of WMH volumes was to estimate the white matter area in each subject using atlas-based segmentation. A probability map of white matter was previously created from 313 volunteers aged 18-96 years[19] and registered to each subject using non-linear (diffeomorphic) registration to provide an initial estimate of white matter in each subject[20]. Hyperintense outliers were identified on T2 FLAIR by transforming each voxel to a standard (z) score[21]. Voxels with $z \geq 1.5$ and within the estimated white matter area were initially defined as WMH. Final WMH estimates were defined by 3D Gaussian smoothing to reduce noise and account for partial volumes around WMH edges. Automatic WMH estimates were visually checked and stroke infarcts masked by a trained image analyst following STRIVE guidelines[22]. Normal-appearing tissues including cortical grey matter (GM), sub cortical GM, cerebral normal appearing white matter (NAWM) and supratentorial cerebrospinal fluid (CSF) were segmented using population specific tissue probability maps, within-patient T1 intensity data and adjoining voxel data. Normal appearing tissue segmentations were checked and edited in the same manner as WMH.

Measures of cerebral diffusion included fractional anisotropy (FA) and mean diffusivity (MD) that were calculated from the eigenvalues (magnitude of water movement in each diffusion direction) obtained with diffusion MRI. The BrainSuite Diffusion Pipeline (BDP)[23,24] corrected geometric distortions in diffusion images and

co-registered diffusion and structural images. FA and MD were calculated in regions of WMH and NAWM.

Change in modality of renal replacement therapy

The primary aim of our study is to observe the effect of hemodialysis treatment on cerebral function and structure. However, we acknowledged many patients suitable for recruitment may be listed for renal transplantation. Therefore, patients who remained on hemodialysis and those who received a renal transplant remained under follow-up. Death, patient request or use of peritoneal dialysis resulted in withdrawal from the study. A flow chart outlining recruitment, follow-up and testing is available in supplementary data, figure s1.

Statistical Analyses

Baseline demographic variables are presented as medians and compared using Mann-Whitney U or Chi-squared as appropriate.

Primary Analyses

Our primary aim was to describe alterations in cerebral blood flow and correlate this with intradialytic cognitive variation. Thus, mean flow velocity is presented as a median of MFV of all patients, demonstrating the change of MFV throughout the dialysis session. We applied a weighted generalised estimating equation (GEE) to model change in MFV, which had small amounts of missing data missing at random, supplementary table s2. Cognitive scores are paired data, comparing either on or off dialysis or again at 12 months follow-up, thus the Wilcoxon Signed Rank test is used. Correlation between %decline in MFV, dialysis-related variables and change in cognitive score were performed using Spearman’s rank correlation. Multiple

cognitive tests were correlated against change in MFV. To account for multiple comparison errors we have provided both the Bonferroni and false discovery rate (FDR) correction, highlighting significant values within each table. Further details are provided in supplementary data, tables s3-4.

Secondary Analyses

At follow-up the cohort was divided into those remaining on hemodialysis and those with a renal transplant for comparison. Cognitive assessments off dialysis were compared at 0 and 12 months using Wilcoxon Signed Rank test and correlation with baseline %decline in MFV assessed using Spearman's rank correlation. Changes in MR imaging findings at 0 and 12 months are also paired and so compared using Wilcoxon Sign Rank test and correlated with changes in cognitive assessment as above. Selected correlation plots are available in supplementary data, supplementary figures 2-5.

Statistical analyses were performed on SPSS version 24 (IBM, Armonk, New York) and the GEE was implemented using the "PROC GEE" statement in the Statistical Analysis System (SAS) version 9.4 (© 2002-2012 SAS Institute Inc.).

Power calculations

To assess cognitive function we calculated 73 patients would be required to show that a decline in HD, based on published baseline ranges of a mean rescaled executive function of 8.7 (SD 2.8)[3] and assuming a decline of 1 during follow up, with SD of mean of 3. To allow for 25% drop out, we aimed to recruit 97 patients.

The primary analysis for the MRI study is to detect correlation between TCD and MRI findings as WMH lesion burden. To detect correlation r (r=0.5), using a two-

sided test at 5% significance with 80% power, the required sample size is 29. To allow for 25% drop out (death and renal transplant), 40 patients will be recruited.

Results

Ninety seven patients were recruited, median [IQR] age 59 [51, 67] years. 40 (41.2%) were female and 32 (33%) diabetic. Median duration [IQR] of dialysis at first visit was 1.76 [0.6, 4.0] years. Eighty-eight patients completed both baseline intra- and inter-dialytic visits. Median [IQR] duration between baseline visits was 27 [22, 34] days.

Cognitive Impairment at baseline off dialysis

Cognitive impairment was present in 43 (48.9%) of this population who were not known to have cognitive impairment, based on MOCA<26. Demographics are demonstrated in table 1. Those with cognitive impairment were more likely to have evidence of systolic hypertension; pre-dialysis systolic blood pressure 148.8vs 133.5mmHg, p=0.02. There were no differences in age or duration of ESRD.

Hemodialysis and Cerebral Blood Flow

Insonation of ≥1 middle cerebral artery was possible in 82 participants, being not-visible or deemed unreliable in the remainder. 18 of 82 were unable to continuously wear the headset throughout dialysis: in 8 participants the headset was ill-fitting or uncomfortable and a further 10 participants requested removal within the first 2 hours, with 6 complaining of a headache, relieved immediately on removal. Mean flow velocity (MFV) declined following dialysis remaining lower up to 30 minutes after completion of dialysis, median MFV reading 47.38 to 40.75 cm/s, p<0.001, figure 1. The median [IQR] %decline was -10[-21.9, 0.0] %. The %decline in MFV correlated with UF volume and rate and change in weight, rho 0.512, 0.493 and 0.463 respectively, p<0.001 but not change in absolute blood pressure values. Change in

mean arterial pressure and presence of diabetes weakly correlated with a %decline in MFV, table 2.

Cognitive Function: on and off dialysis assessments

Compared to their assessments during an off-dialysis period, participants scored lower in assessments of executive function during dialysis; processing speed (LDST), 22 vs 24.5, $p<0.001$ and attention/task switching (TMTB), time-taken 88.5 vs 75 sec, $p<0.001$, table 3.

Significant correlations between the %decline in MFV during dialysis and a decline in TMTA, rho -0.454, $p<0.001$, TMTB, rho -0.323, $p=0.01$ and phonemic fluency, rho 0.302, $p=0.01$ during dialysis were detected. Further, worsening scores on global cognitive assessment (MOCA) during dialysis correlated with %decline in MFV (rho 0.270, $p=0.02$), table 3.

Follow-up

Median [IQR] follow-up was 1.05 [1.0, 1.1] years. At follow-up, 15 participants had been transplanted, 4 withdrew and 6 died (supplementary data, figure s1). Those who were transplanted were younger, median [IQR] 51 [40, 63] vs 60 [52, 67] years and had a shorter duration of ESRD, median [IQR] 0.6 [0.2, 1.6] vs 2.1 [0.7, 4.5] years, supplementary table s5. Paired 0 and 12 month inter-dialytic assessments were possible in 61 of those who remained on HD and 12 who received a kidney transplant. Baseline and follow-up MRI data were available in 24 who continued HD and 10 who were transplanted.

Cognitive function at follow-up: continued hemodialysis vs transplanted

At 12 months follow-up those who remained on dialysis had an improvement in MOCA score, 26 vs 24, p<0.01. No other assessment revealed significant differences. In contrast, those who underwent transplant had no change in their MOCA score, 26 vs 26, p=0.23, but demonstrated an improvement in verbal memory: delayed recall, 9.5 vs 6.5, p=0.02; retention, 100 vs 68.3%, p=0.03 and discrimination, 11 vs 10, p=0.03, table 4.

In those who remain on dialysis %decline in MFV was significantly correlated with worsening score in global cognitive function (MOCA) and executive function (TMTB) on follow-up, rho 0.276 p=0.043 and rho -0.403, p=0.005 respectively, table 4.

In those who received a transplant an observed %decline in MFV correlated with worsening phonemic fluency at follow-up, rho 0.758. p=0.011, table 4.

MR derived structural Changes

In those who continued on dialysis, progressive lobar atrophy was evident in frontal, parietal and temporal lobes, p<0.05, table 5. White matter hyperintensity burden increased, 2.96-3.36mL, p=0.018, figure 2. There were no changes in DTI measures, FA and MD, table 5.

Following kidney transplant, a similar pattern of lobar atrophy was noted. However, there was no progression in WMH burden. Fractional anisotropy in white matter increased, 0.28 - 0.29, p=0.016, table 5.

Correlating structural changes with cognitive function

There was no correlation between %decline in MFV assessed at baseline and MRI findings.

In those who continue dialysis greater frontal atrophy correlates with worsening score in global cognitive and executive function, MOCA, rho 0.454, p=0.04, TMTB – rho 0.620, p=0.01 and auditory-verbal memory, rho 0.805, p=0.01. An increase in WMH burden correlates with verbal fluency and mood, rho 0.585, p=0.01 and rho -0.485, p=0.03, table 6.

In who received a kidney transplant, an increase in WMH burden correlates with worsening executive function, TMTB rho -0.81, p=0.015. In contrast, an increase in fractional anisotropy correlates with an improvement in executive function, LDST rho -0.886, p=0.019. Surprisingly, worsening frontal atrophy correlated with improvement in executive function.

Discussion

This prospective study of people with ESRD encompassing blood flow, functional and structural assessments of the brain has several important findings. Firstly, we demonstrated that cerebral blood flow declines during dialysis, correlating with ultrafiltration volumes and with a measurable decline in executive function. At follow-up, a correlation was detected between reduced cerebral blood flow and executive function in those who remained on dialysis but not those who were transplanted. Following transplant, verbal learning and memory improved. Finally, brain MRI revealed progressive WMH burden in those who remain on dialysis, but not those were transplanted. In contrast, after transplantation increased fractional anisotropy of the white matter correlated with improved executive function.

We believe this study supports the hypothesis that hemodialysis may be associated with short-term 'cerebral-stunning' and demonstrates progressive injury in those who remain on dialysis, whereas there is a demonstrable improvement in memory and white matter integrity in those who are transplanted. Early recognition of those at risk may limit this cerebral injury, which appears potentially reversible by transplantation.

Cognitive function in ESRD: incidence and consequences

We have demonstrated in a 'low-risk' HD population, without recorded cerebrovascular disease or cognitive impairment, that mild cognitive impairment is present in 48.9%. Once end-stage renal disease is established, it is estimated that up to 70% of those on HD have cognitive impairment [1]. Surprisingly, in that particular study only ~3% had documentation of cognitive impairment. We demonstrated intradialytic cerebral blood flow declines with increasing ultrafiltration volumes

Therefore, in ESRD, failure to recognise cognitive impairment could perpetuate future cognitive decline; due to cognitive impairment patient concordance with fluid restriction is poor , a necessary increase in ultrafiltration volumes compromise cerebral circulation cognition worsens and concordance worsens still. . Morbidity aside, cognitive dysfunction is also associated with all-cause mortality[25,26] and dialysis withdrawal[27].

Dialysis and Cognitive Dysfunction

Multiple factors are reported to influence cognitive function in CKD. Conventional risk factors such as age, diabetes, hypertension and dyslipidaemia are abundant however unconventional 'renal' factors including treatments for CKD e.g. the historical effect of aluminium toxicity[28] or more recently the effect of dialysis itself are implicated[2,29–31]. In contrast to neurodegenerative cognitive disorders where memory is predominantly affected, the pattern of cognitive impairment most commonly described in those with CKD is loss of executive function[2–4], a phenotype associated with vascular cognitive impairment. Further, more intensive dialysis does not improve function[6,7]. This has led to the conclusion that cognitive impairment is driven by cerebrovascular disease.

Previous data on cognitive variation around the dialysis session are conflicting. Authors have described both improvements[31,32] and worsening[30] of post dialysis cognition. We believe we are the first study to correlate an acute change in cerebral blood flow with real-time alterations in cognitive function. This has several important implications. Immediately, clinicians should be aware that detailed clinical discussions should not be undertaken during hemodialysis as comprehension and recall maybe affected. Further, this must prompt additional research designed to limit

the damage observed on MRI. One clinical trial has demonstrated using dialysate cooling can provides stability in white matter integrity at one year[33]. The beneficial cognitive effects of renal transplantation require further attention and the benefit of expediting transplantation as a treatment for early cognitive dysfunction should not be overlooked.

Transplantation and Cognitive Dysfunction

Renal transplantation remains the 'gold standard' treatment for ESRD[34] . Transplantation reduces the risk of cardiovascular disease[35], increasing life expectancy and improves quality of life[36]. In our study we have observed, as others have[37–39], an improvement in cognitive function following transplantation, specifically memory albeit in a small cohort of our patients. Fractional anisotropy is a marker of white matter integrity and deficits in diffusion are recognised to precede white matter hyper intensity formation and are associated with worsening executive function[40]. In those who received a renal transplant, FA improved and correlated with improved executive function, whereas there was no demonstrable improvement in anisotropic diffusion in those remaining on hemodialysis. Previous authors have demonstrated improvement in executive function following transplantation[38], a finding that does not appear to achievable by more frequent dialysis. In an analysis of participants in the Frequent Hemodialysis Network an improvement in auditory-verbal memory and processing speed was observed following transplantation, but not after 12 months of frequent hemodialysis (6 days/week)[7]. This is supportive of a 'side-effect' produced by HD, ameliorated by transplantation.

Limitations

This prospective observational cohort study has demonstrated important findings in a real-world ESRD cohort. However, we recognise the following limitations. As an observational study we cannot prove causation due to inability to account for unmeasured variables. For example, we do not have bicarbonate or blood viscosity levels which may be of greater significance than ultrafiltration volume on MFV. We excluded those with any known evidence of cerebrovascular disease which resulted in a younger cohort. This reduces generalisability and makes it likely we have underestimated the prevalence of cognitive impairment and the impact of ongoing treatments on more ‘fragile’ brains. Whilst we acknowledge this as a limitation, we also believe this makes our findings all the more striking. No attempts were made to standardise dialysis regimes. Although this could mask findings acutely, we believe this provides a more realistic view of dialysis. Use of transcranial Doppler ultrasound to measure cerebral blood flow has limitations, namely operator variability and absence of acoustic windows. All TCD readings were performed by one trained operator to reduce variation and we acknowledge TCD was not possible in 15 (15%) of our recruited cohort. Our findings are correlated to MFV changes over a single dialysis session, with follow-up spanning an entire year. Generalising one session to an entire year may impact on correlations at follow-up. As TCD measurements were taken at fixed time points it not possible to comment on unrecorded episodes of acute decline in MFV. Finally, throughout this manuscript we refer to cerebral blood flow. It is important to clarify transcranial Doppler measures cerebral blood flow velocity, an indirect measure of cerebral blood flow providing the diameter of the insonated vessel does not change during measurements. It is not known whether hemodialysis alters cerebral vessel diameter.

Attempts were made to limit a learning effect. Namely, multiple versions of MOCA and HVLT were used, a minimum of 14 days between assessments was allowed and visit order was reversed in a randomly selected 20%. Despite our attempts we cannot completely exclude this learning effect. Frontal atrophy correlated with improved executive function in transplanted patients. Whilst frontal atrophy is a marker of aging, and executive function can improve following transplantation[38] it is important to acknowledge our low number of transplant patients at follow-up, which could introduce both type 1 and 2 errors. In particular – this small number may lead to chance association between MR imaging findings and change in cognitive function. We did not detect correlation between MFV and MRI changes. Only 24 patients completed follow-up scans in 24 patients whilst on continued dialysis. Therefore, correlating %decline MFV with MRI findings is underpowered and may account for the lack of effect. Finally, and with particular reference to the young age of our cohort, we did not detect progressive cognitive dysfunction – rather improvement in MOCA score at 12 months in those on continued dialysis. It is likely that the follow-up time was too short to detect a measurable difference in cognitive function in this recruited cohort.

Conclusions

Our study has highlighted the high frequency of occult cognitive impairment, affecting 50% of our prevalent dialysis cohort without known cerebrovascular disease. Hemodialysis is capable of inducing a transient decline in cerebral blood flow, correlating with intradialytic cognitive dysfunction. Evidence of progressive cerebrovascular disease is demonstrated in those who remain on dialysis, whereas following transplantation improvement in cognitive function and cerebral anisotropic

diffusion is suggestive of reversibility. Urgent interventions are required to limit cerebral stunning and prevent progressive cognitive decline.

Author Contributions

MDF, JD and PBM had the original idea. MDF, TQ and DM coordinated data collection. DD was responsible for producing outputs following MR image analyses and contributed to the statistical analysis. MDF analysed the data and constructed the first draft. All authors contributed to the final draft.

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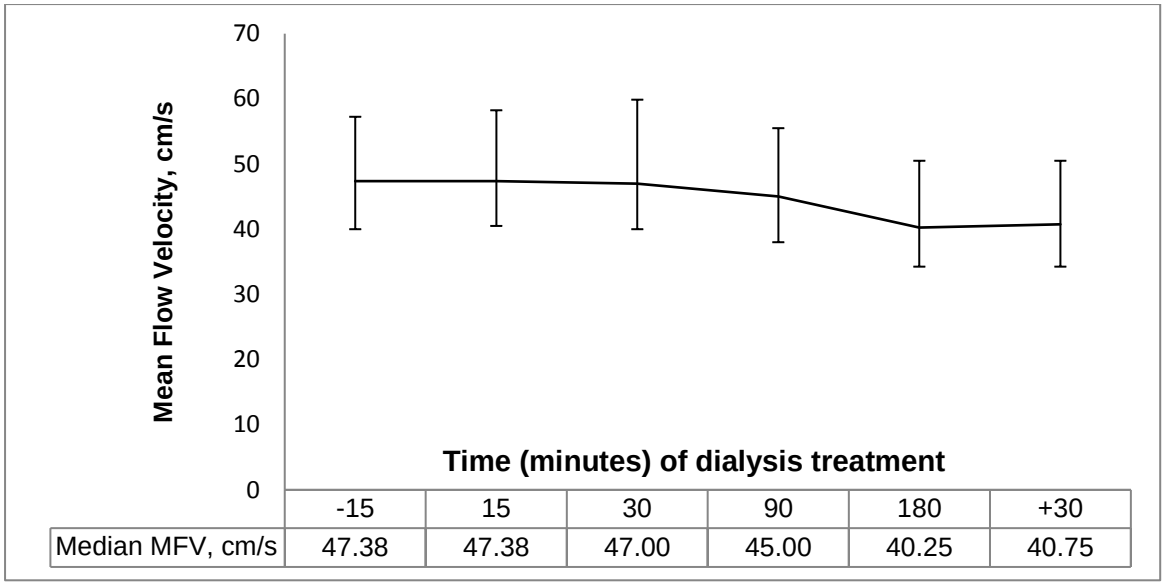
	No Cognitive Impairment	Cognitive Impairment	ALL	p-value
Median age, years [IQR]	58 [49,66]	58 [51,67]	58 [50.5,66.5]	0.61
Female, n [%]	20 [44.4]	15 [34.9]	35 [39.8]	0.36
Active on Transplant Waiting list. n [%]	20 [44.4]	17 [39.5]	37 [38.6]	0.64
Ethnicity. n [%]				
European	43 [95.6]	41 [95.3]	84 [95.5]	
Asian	2 [4.4]	2 [4.7]	4 [4.5]	0.96
Primary Renal Diagnosis. n [%]				
Diabetes	8 [17.8]	10 [23.3]	18 [20.5]	
Glomerulonephritis	8 [17.8]	11 [25.6]	19 [21.6]	
Interstitial	11 [24.4]	5 [11.6]	16 [18.2]	
Multisystem	7 [15.6]	10 [23.3]	17 [19.3]	
Other	11 [24.4]	7 [16.3]	18 [20.5]	0.36
Past Medical History. n [%]				
Hypertension	37 [82.2]	41 [95.2]	78 [88.6]	0.05
Diabetes mellitus	14 [31.1]	15 [34.9]	29 [33.0]	0.71
Ischemic heart disease	11 [24.4]	8 [18.6]	19 [21.6]	0.51
Congestive cardiac failure	3 [6.7]	6 [14.0]	9 [10.2]	0.26
Peripheral Vascular disease	3 [6.7]	3 [7.0]	6 [6.8]	0.95
Atrial Fibrillation	5 [11.1]	4 [9.3]	9 [10.2]	0.78
Depression	8 [17.8]	10 [23.3]	18 [20.5]	0.52
Duration of ESRD, years [IQR]	1.39 [0.61,3.34]	1.92 [0.52,4.39]	1.62 [0.57,4.02]	0.84
Dialysis Related Variables, median [IQR]				
Pre-SBP, mmHg	133.5 [120.8,153.3]	148.8 [129.3,168.0]	143.5 [121.4,158.5]	0.02
Pre-DBP, mmHg	70.8 [65.2,81.7]	74.8 [65.0,79.8]	73.1 [65.1,80.7]	0.61
Post-SBP, mmHg	122.7 [112.4,143.8]	135.7 [118.2,158.0]	130.7 [113.4,148.5]	0.03
Post-DBP, mmHg	68.0 [59.5,80.2]	71.2 [61.0,77.7]	69.3 [60.1,78.2]	0.59
UF Volume, L	2.0 [1.3,2.4]	2.1 [1.4.2.9]	2.1 [1.4,2.6]	0.13
UF Rate, mL/hour	-442.1 [-240.0,-575.0]	-500.0 [-350,-622.2]	-484.4 [-261.9,-484.4]	0.32
Dialysis Access. n [%]				
AV access	34 [75.6]	28 [65.1]	62 [70.5]	
Central Venous Catheter	11 [24.4]	15 [34.9]	26 [29.5]	0.28
Median Laboratory Values [IQR]				
Serum Adjusted Calcium, mmol/L	2.39 [2.29,2.46]	2.37 [2.27,2.45]	2.38 [2.28,2.46]	0.59
Serum Phosphate, mmol/L	1.76 [1.42,2.03]	1.74 [1.49,2.04]	1.75 [1.47,2.04]	0.90
Hemoglobin, g/L	117.7 [106.7,122.7]	110.7	113 [102.2,122.0	0.13
Serum Albumin, mmol/L	33.0 [31.7,35.3]	[101.0,120.33]	33.2 [30.8,35.0]	0.94
PTH, nmol/L	68.6 [42.6,98.2]	33.3 [29.7,34.3]	61.6 [37.4,99.0]	0.31
Urea Reduction Ratio	71.5 [69,77]	53.3 [32.3,103.5] 73.5 [70.0,76.0]	72.8 [69.5,77.0]	0.58
Median Years of Education [IQR}	12 [11.0,13.5]	12 [11.0,14.0]	12 [11,14]	0.71

Table 1 Demographics of study cohort, split by presence or absence of mild cognitive impairment using MOCA score <26 on baseline non-dialysis day assessment, n=88. Abbreviations: ESRD, end-stage renal disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; UF, ultrafiltration; AV, arteriovenous; PTH, parathyroid hormone.



	-15	15	30	90	180	+30
Median MFV, cm/s	47.38	47.38	47.00	45.00	40.25	40.75

Figure 1 Change in mean flow velocity during diaysis session, n=82, described as median value and interquartile range (error bars). Transcranial doppler recordings were taken prior, during and after completion of dialysis, demonstrating a significant decline in MFV following dialysis, weighted generalised estimating equation $p<0.0001$. Abbreviations: MFV, mean flow velocity.

Variable	Spearmann's Rho	p-value
Ultrafiltration volume, mL	0.512	<0.001
Ultrafiltration rate, mL/hr	0.493	<0.001
Delta SBP, mmHg (pre-post)	0.196	0.08
Delta DBP, mmHg (pre-post)	0.163	0.14
Delta Weight, kg (pre-post)	0.463	<0.001
Delta MAP, (pre-post)	0.219	0.048
Diabetes mellitus	-0.304	0.005

Table 2 Clinical variables and their correlation to %decline in middle cerebral artery mean flow velocity, n=82. Delta values are calculated as pre minus post values, therefore the greater the fall after dialysis the higher the value. A positive correlation denotes as % decline becomes more positive (i.e. a greater decline in MFV) the associated variable becomes more positive. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Assessment, n=88	Intradialytic Assessment	Interdialytic Assessment	p-value	Correlation with % decline MFV, Rho	p-value
Global Cognitive Function					
MOCA	25.0 [22.0,27.0]	25.0 [21.5,27.0]	0.44	0.270	0.02[2]
Verbal Fluency					
Semantic	18.0 [14.5,21.5]	18.0 [15.0,22.0]	0.28	0.172	0.14
Phonemic	33 [26.0,41.5]	34.0 [25.0,43.5]	0.49	0.302	0.01[2]
Executive Function					
TMTA	38.0 [26.5,51.0]	35.5 [26.9,50.0]	0.63	-0.454	<0.001[1, 2]
TMTB	88.5 [62.0,136.0]	75.0 [54.0,112.0]	<0.001	-0.323	0.01[2]
LDST	22.0 [18.0,27.0]	24.5 [20.0,30.0]	<0.001	-0.170	0.15
Auditory-Verbal Memory					
HVLT					
Total Recall	22.0 [19.5,25.5]	20.0 [17.0,23.0]	<0.001	0.089	0.45
Delayed Recall	7.0 [5.0,9.0]	6.0 [4.0,9.0]	0.13	0.098	0.41
Retention	80.0 [60.0,90.0]	80.0 [60.0,100.0]	0.60	-0.046	0.70
Discrimination	10.0 [9.0,11.0]	10.0 [9.0,11.0]	0.90	0.057	0.63
Mood					
CES-D	8.0 [4.0,17.0]	9.0 [4.0,17.5]	0.80	0.097	0.41

Table 3 Differences in cognitive scores during and outwith dialysis, n=88, and correlation between %decline in MFV and cognitive scores. Difference in cognitive score is calculated as non-dialysis score minus dialysis score. Positive rho = as %decline increases (i.e. a greater fall in MFV) the difference in cognitive scores becomes more positive. In the above tests a positive difference in cognitive score describes a lower cognitive score during dialysis, with the exception of TMTA, TMTB and CES-D where the inverse is true. Correlations which remain significant following Bonferroni correction are marked with superscript [1], and FDR [2]. Abbreviations: MOCA, Montreal Cognitive Assessment; LDST, letter-digit substitution test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; HVLT, Hopkins Verbal Learning Test; CES-D, Centre for Epidemiologic Studies Depression Scale; FDR, false detection rate.

Assessment	Baseline Assessment	Follow-up Assessment	p-value	Correlation with %declineMFV, Rho	p-value
Continued Hemodialysis, n=61					
MOCA	24.0 [21.0,27.0]	26.0 [23.0,28.0]	<0.01	0.276	0.043
Semantic	19.0 [15.0,21.0]	18.0 [15.0,21.0]	0.45	0.201	0.15
Phonemic	35.0 [28.0,44.0]	37.0 [27.0,46.0]	0.06	0.150	0.28
LDST	24.0 [20.0,31.0]	26.0 [20.0,31.0]	0.87	-0.085	0.55
TMTA	34.0 [26.0,47.0]	31.0 [26.0,45.0]	0.09	-0.209	0.15
TMTB	71.0 [49.0,99.0]	66.0 [49.0,99.0]	0.90	-0.403	0.005[2]
HVLT					
Total Recall	20.0 [17.0,23.0]	21.0 [17.0,26.0]	0.28	0.098	0.48
Delayed Recall	7.0 [4.0,10.0]	7.0 [4.0,9.0]	0.97	0.243	0.08
Retention	80.0 [62.5,100.0]	80.0 [55.6,90.9]	0.45	0.219	0.15
Discrimination	11.0 [9.0,12.0]	11.0 [9.0,12.0]	0.92	0.149	0.30
CES-D	10.0 [5.0,18.0]	10.0 [4.0,18.0]	0.59	0.139	0.32
Transplanted at follow-up, n=12					
MOCA	26.0 [24.5,27.0]	26.0 [25.0,28.5]	0.23	0.086	0.81
Semantic	18.0 [15.5,26.0]	21.0 [20.5,23.5]	0.42	0.609	0.06
Phonemic	33.5 [28.5,46.0]	36.0 [28.5,42.0]	0.96	0.758	0.011
LDST	31.0 [26.0,35.0]	33.0 [26.0,35.0]	0.43	0.383	0.28
TMTA	35.0 [26.0,37.0]	34.5 [20.5,41.0]	0.63	-0.500	0.17
TMTB	63.0 [51.0,108.0]	58.0 [45.0,82.0]	0.33	-0.317	0.41
HVLT					
Total Recall	21.0 [17.5,24.0]	22.5 [19.5,27.5]	0.35	0.329	0.35
Delayed Recall	6.5 [4.5,8.0]	9.5 [7.0,10.0]	0.02	-0.123	0.74
Retention	68.3 [59.8,94.4]	100.0	0.03	-0.358	0.31
Discrimination	10.0 [10.0,11.0]	[79.8,105.0]	0.03	0.273	0.45
		11.0 [10.5,12.0]			
CES-D	6.5 [1.0,13.0]	2.5 [1.0,8.0]	0.31	-0.334	0.35

Table 4 Differences in cognitive scores at baseline and follow-up (using interdialytic assessments) and correlation between %decline in MFV and cognitive scores in those remaining on hemodialysis and those receiving a kidney transplant. Difference in cognitive score is calculated as baseline minus follow-up score. Therefore, positive rho value = as %decline increases (i.e. a greater fall in MFV) difference in cognitive change becomes more positive. In the above tests a positive difference in cognitive score denotes deterioration at follow-up, with the exception of TMTA, TMTB and CES-D where the inverse is true. Correlations which remain significant following Bonferroni correction are marked with superscript [1], and FDR [2]. Abbreviations: MOCA, Montreal Cognitive Assessment; LDST, letter-digit substitution test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; HVLT, Hopkins Verbal Learning Test; CES-D, Centre for Epidemiologic Studies Depression Scale; FDR, false detection rate.

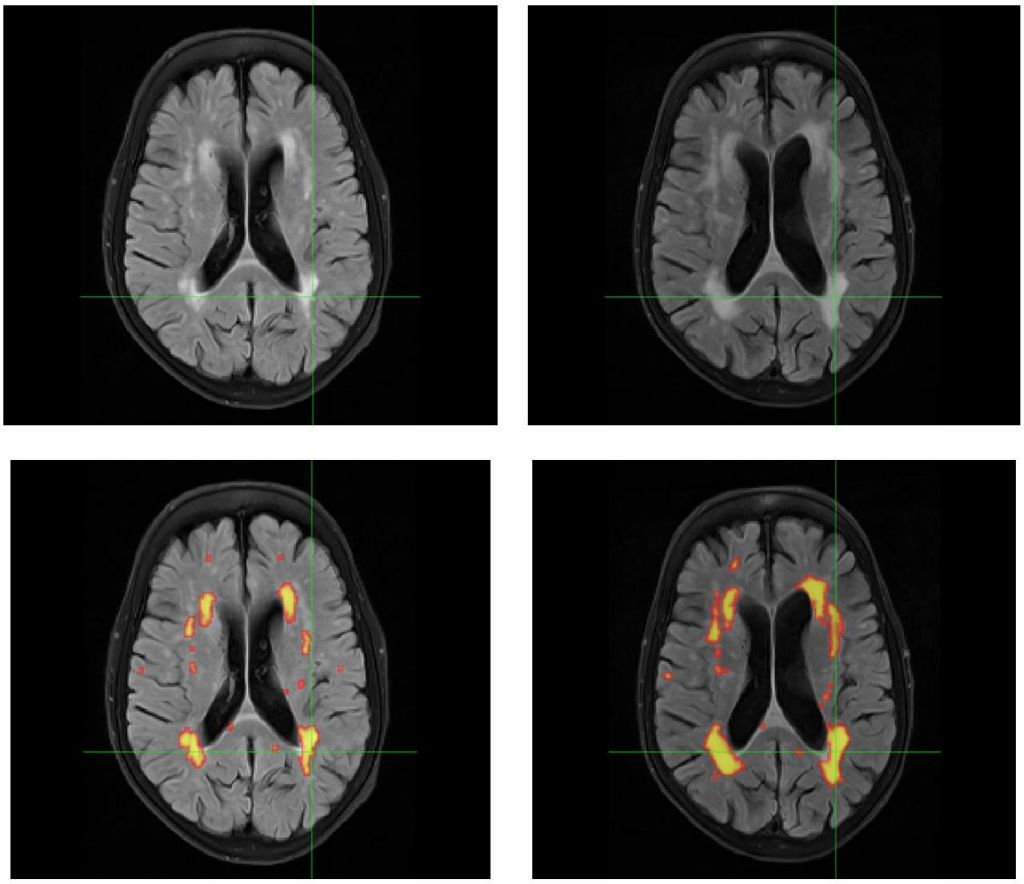


Figure 2 Progression of periventricular white matter hyperintesities (WMH) over 12 months in a patient on continued hemodialysis, baseline images on left, follow-up on right.Additionally, a loss of cerebral volume can be appreciated as enlargement of lateral ventricles. Figure demontrates visible progression of WMH on standard T2 FLAIR sequences (top row) and after application of volumetric analyses software (bottom row).

Assessment	Baseline Assesment	Follow-up Assesment	p-value
Continued Hemodialysis, n=24			
Median Lobar Vol. (mL)			
Frontal GM	160.3 [150.8,166.3]	155.2 [147.4,162.3]	0.015
Parietal GM	93.9 [89.1,102.6]	92.9 [85.4,99.2]	0.028
Temporal GM	116.8 [110.5,122.8]	111.3 [105.6,121.6]	0.009
Occipital GM	60.4 [55.2,65.9]	58.3 [54.8,63.6]	0.08
WMH Volume, mL	2.96 [0.87,6.07]	3.36 [0.82,7.35]	0.018
DTI			
FA_WM	0.27 [0.02]	0.26 [0.02]	0.41
FA_WMH	0.26 [0.04]	0.26 [0.03]	0.64
MD_WM $10^3m^2/s$	0.9 [0.1]	0.9 [0.1]	0.19
MD_WMH $10^3m^2/s$	1.2 [0.01]	1.2 [0.1]	0.05
Transplanted at follow-up, n=10			
Median Lobar Vol. (mL)			
Frontal GM	166.9 [159.9,185.0]	162.2 [157.4,186.4]	0.028
Parietal GM	102.6 [98.1,114.8]	101.6 [97.8,112.2]	0.047
Temporal GM	115.0 [111.6,136.6]	113.8 [108,134.5]	0.009
Occipital GM	64.2 [60.1,75.6]	64.8 [59.7,73.9]	0.33
WMH Volume, mL	1.02[0.79,2.01]	1.17 [0.64,1.25]	0.24
DTI			
FA_WM	0.28 [0.01]	0.29 [0.01]	0.016
FA_WMH	0.25 [0.03]	0.26 [0.03]	0.07
MD_WM $10^3m^2/s$	0.8 [0.01]	0.8 [0.02]	0.62
MD_WMH $10^3m^2/s$	1.1 [0.1]	1.1 [0.1]	0.72

Table 5 Differences in neuroimaging parameters at baseline and follow-up in those who remain on dialysis and those who received a kidney transplant. Abbreviations: GM, Grey Matter; WMH, White matter hyperintensities; DTI, Diffusion Tensor Imaging; FA_WM, Fractional Anisotropy in white matter; FA_WMH, Fractional Anisotropy in white matter hyperintesities; MD_WM, Mean diffusivity in white matter; MD_WMH, Mean diffusivity in white matter hyperintensities

Assessment	Correlation with ΔWMH	p-value	Correlation with ΔFA_WM	p-value
Continued Hemodialysis, n=21				
MOCA	0.172	0.46	0.225	0.48
Semantic	-0.028	0.90	-0.175	0.59
Phonemic	0.585	0.01	-0.365	0.24
LDST	0.129	0.58	0.116	0.72
TMTA	0.328	0.16	-0.278	0.41
TMTB	-0.384	0.12	-0.103	0.78
HVLT				
Total Recall	0.271	0.23	0.327	0.30
Delayed Recall	0.268	0.24	0.160	0.62
Retention	0.172	0.46	0.056	0.86
Discrimination	0.296	0.19	-0.381	0.22
CES-D	-0.485	0.03*	0.140	0.66
Transplanted at follow-up, n=9				
MOCA	-0.092	0.81	0.319	0.54
Semantic	-0.301	0.43	-0.600	0.21
Phonemic	0.460	0.21	-0.667	0.15
LDST	-0.101	0.80	-0.886	0.019
TMTA	0.071	0.87	0.200	0.75
TMTB	-0.810	0.015	-0.600	0.29
HVLT				
Total Recall	0.025	0.95	-0.232	0.66
Delayed Recall	0.522	0.15	0.353	0.49
Retention	0.483	0.19	-0.143	0.79
Discrimination	-0.173	0.65	0.152	0.77
CES-D	0.460	0.21	-0.143	0.79

Table 6 Correlations of changes in neuroimaging with change in cognitive testing over 12 months, in those who remain on hemodialysis and those receiving a kidney transplant. For all neuroimaging results, values are = follow-up minus baseline, hence a reduction in value with time will produce a negative result. As previous, difference in cognitive score is calculated as baseline minus follow-up score. Therefore, positive rho = positive neuroimaging change relates to a positive cognitive score at follow-up. In the above tests a positive follow-up cognitive score denotes deterioration, with the exception of TMTA, TMTB and CES-D where the inverse is true. Abbreviations: WMH, White matter hyperintesities; FA_WM, Fractional anisotropy in white matter; MOCA, Montreal Cognitive Assessment; LDST, letter-digit substitution test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; HVLT, Hopkins Verbal Learning Test; CES-D, Centre for Epidemiologic Studies Depression Scale