

Cognitive function declines significantly during haemodialysis in a majority of patients:

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DOI:
[10.1159/000485961](https://doi.org/10.1159/000485961)

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Dasgupta, I, Patel, M, Mohammed, N, Baharani, J, Subramanian, T, Thomas, GN & Tadros, G 2018, 'Cognitive function declines significantly during haemodialysis in a majority of patients: a call for further research', *Blood Purification*, vol. 45, no. 4, pp. 347-355. <https://doi.org/10.1159/000485961>

[Link to publication on Research at Birmingham portal](#)

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Title: Cognitive function declines significantly during haemodialysis in a majority of patients: A need for further research

Running Head: Cognitive decline over haemodialysis

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Support: Authors received no grant support for this study.

Financial disclosures and conflicts of interest: None

Key words: cognition, dementia, haemodialysis, MOCA

Abstract:

Introduction: Cognitive impairment (CI) is very common in haemodialysis patients and associated with reduced functional capacity and mortality. We assessed change in cognitive function during haemodialysis and associated risk factors.

Methods: All patients ≥ 50 years, on haemodialysis for ≥ 3 months, no dementia from 2 dialysis centres were selected. Cognition was assessed before and after a haemodialysis session using parallel versions of Montreal Cognitive Assessment (MOCA) tool. Multiple regression was used to examine potential confounders.

Results: 82 patients completed both tests - median age 73 (52–91) years, 59% male, dialysis vintage 41 (3– 88) months. 62 (76%) had CI at baseline. Cognition declined over dialysis (MOCA 21 ± 4.8 to 19.1 ± 4.1 , $p < 0.001$), domains affected were attention, language, abstraction and delayed recall. Age and dialysis vintage were independently associated with decline.

Conclusion: Cognitive function declines over a haemodialysis session that has significant clinical implications for health literacy, self-management and tasks like driving. More research is needed to find the cause of this.

Introduction:

Increasing severity of chronic kidney disease is associated with a graded increase in prevalence of cognitive impairment [1,2] and decrease in brain perfusion independent of vascular risk factors [3]. Cognitive impairment was three times more common in haemodialysis patients than age-matched general population with as many as 70% of haemodialysis patients over the age of 55 years suffering from moderate to severe cognitive impairment [4,5,6]. A recent meta-analysis showed patients treated with haemodialysis have more cognitive impairment than general population with orientation, attention, memory and executive function being more affected [7]. Cognitive function dropped significantly after the start of haemodialysis and progressed in a stepwise fashion. Cognitive impairment in haemodialysis patients was independently associated with higher rates of depression, functional impairment and mortality [4,8].

Clustering of atherosclerotic risk factors [8], cannot entirely account for the excess risk of cognitive impairment in haemodialysis [9]. There are multiple chronic kidney disease and haemodialysis-specific risk factors including oxidative stress, malnutrition and inflammation which may be contributory [10]. Incomplete removal of uraemic toxins by haemodialysis allowed accumulation of neurotoxins [11] that reduced brain perfusion and blood-brain barrier integrity [12]. Moreover, haemodialysis involves repetitive cycles of removing varying volumes of fluid, electrolytes and toxins that accumulate between treatments, which can lead to complications. For instance, hypotension partially results from fluid removal rates exceeding plasma refill rates. Ubiquitous left ventricular hypertrophy and aortic stiffness further lower the threshold for haemodialysis to inflict recurrent multi-organ ischemia-reperfusion injury [13, 14]. Haemodialysis might cause worsening of cognitive impairment by inducing haemodynamic instability, fluid shifts, cerebral ischaemia or cerebral oedema [10,13,15]. These dynamic changes in blood pressure and perfusion might be associated with altered cognition but the data are sparse and conflicting, possibly reflecting differences in study design. Several small studies showed cognitive function was best immediately before haemodialysis, worse during haemodialysis and improved the day after with a possible link to sudden fluid removal or other factor related to the haemodialysis process [4,16-20].

The aim of this study was to assess systematically the change in cognitive function over a single haemodialysis session using the commercially available Montreal Cognitive

Assessment (MOCA) battery [21], and the relationship between this and a number of putative risk factors for cognitive impairment in haemodialysis patients.

Materials and Methods:

Participants and setting:

All patients over the age of 50 years from two satellite haemodialysis centres affiliated to the main renal centre were selected. Patients in satellite centres were chosen because these patients are clinically more stable; satellite dialysis centres are quieter, more spacious with adequate lighting and patients dialyse either in side rooms or in open bays where screens are available to isolate patients for privacy. Inclusion criteria were: being on maintenance haemodialysis for at least 3 months, ability to read and write English, and ability to provide informed consent. Exclusion criterion was a known diagnosis of dementia mentioned in the medical notes. The age cut off 50 years was chosen for cognitive impairment is reportedly more common in haemodialysis patients over this age [5].

Assessment of cognition and physiological parameters:

This was a prospective observational study carried out in March 2014. Cognition was assessed using the Montreal Cognitive Assessment (MOCA) tool carried out by four research assistants who were trained in administering MOCA prior to the study. One researcher (GT) who has vast experience in the use of MOCA in old age psychiatry oversaw four research assistants who carried out the assessments to ensure correct assessment technique and standardization.

MOCA is a validated screening tool for early cognitive impairment in the general population [21]. It has also been validated to screen for cognitive impairment against a battery of neuropsychological tests in haemodialysis patients [22]. It assesses eight cognitive domains, generating a score of between 0 and 30 - Visuospatial/ Executive 5, Naming 3, Memory 0, Attention 6, Language 3, Abstraction 2, Delayed recall 5, Orientation 6. The cut off for normal cognition is 26 for the general population [21] and 24 for haemodialysis patients with a score <17 considered as severe cognitive impairment [22]. Three parallel English versions were used for reassessment to avoid any learning effect. The visuospatial domain of MOCA was marked by an independent person who was not part of the research team.

For each assessment the patient was allowed up to 30 minutes. The first assessment (MOCA 1) was done either before the start of dialysis session or within the 1st half hour of treatment. The second assessment was done in the last half hour of a dialysis session or after needles were withdrawn (MOCA 2). The assessment was done either at the 2nd or the 3rd dialysis session of the week depending on patient preference. All patients were in either morning or the afternoon shifts of dialysis programme. No medications were administered during dialysis with the exception of paracetamol if required. A third cognitive assessment was done a week later before dialysis (MOCA 3) in those agreeing to have a further assessment.

We used the 15-item version of the Geriatric Depression Scale (GDS-15) and the Short Confusion Assessment Method (CAM; four items) to rule out depression and delirium [23,24]. All three assessments were performed before the start of a haemodialysis session and only MOCA was repeated at the end of the same haemodialysis session.

Pre- and post-dialysis body weight, ultrafiltration volume, blood pressure, heart rate and oxygen saturation; and symptomatic and asymptomatic intradialytic hypotensive episode (blood pressure drop from baseline -of ≥ 20 mmHg) of each participant were obtained over the same dialysis session. Demographic details, educational status, comorbidities including diabetes status and cardiovascular disease, smoking status, use of psychoactive drugs (including antihistamines, sedatives, anti-Parkinsonism and psychotropic drugs), type of dialysis fluid used, and laboratory parameters (haemoglobin, white cell count, Kt/V, serum urea reduction ratio, sodium, potassium, calcium, phosphate, ferritin, bicarbonate and albumin [all taken pre-dialysis]) were extracted from the electronic database. In addition, duration of dialysis (in minutes), blood flow rate, dialysate type and dialysate temperature were recorded. As per unit protocol, all patients received haemodialysis (none had haemodiafiltration) for 240 minutes each using a dialysate temperature of 36 degrees centigrade. Also per protocol, all patients were advised to take antihypertensive medications at night so as to avoid intra-dialytic hypotension.

Statistical Analysis:

Cognitive functions based on the MOCA scores, before and after a single haemodialysis session, were compared using a paired t-test. In addition, individual domains of cognitive function before and after the single haemodialysis session were compared using a paired t-test or Wilcoxon signed-rank test for matched-pairs depending on whether scores were

(approximately) normally distributed. The domains included visuo-spatial, memory, naming, attention, language, abstraction, delayed recall and orientation. The relationship between cognitive impairment (based on change in MOCA scores before and after haemodialysis, represented as MOCA 1 and MOCA 2 respectively) and the putative risk factors was examined using linear regression models using two approaches. Firstly, the factors considered include age, sex, smoking status, use of psychoactive drugs, comorbidity score (Charlson Index), cerebrovascular disease, [diabetes](#), dialysis vintage, haemoglobin, total white cell count, serum urea, sodium, potassium, calcium, phosphate, albumin, bicarbonate, ferritin, and changes in weight ([predialysis – postdialysis](#)), [ultrafiltration volume and rate](#), [predialysis](#) systolic blood pressure, heart rate, oxygen saturation, ~~and number of~~ symptomatic [and asymptomatic](#) hypotensive episodes ([intradialytic systolic BP drop ≥20 mmHg](#)), [dialysis blood flow rate and dialysate composition](#). Given that we were exploring a large number of variables relative to the sample size, we adopted a systematic approach to select only variables that were significant in univariate analyses before fitting the final regression models. Secondly, as confounding can both exaggerate or mask potential associations, we, a priori, identified nine variables that we considered to be biologically important to our hypothesis and incorporated those in a sensitivity analysis using a multiple linear regression model irrespective of their significance in univariate modelling. The variables included were age, sex, dialysis vintage, Charlson score, cerebrovascular disease, use of sedating drugs, change in BP, change in weight. The model was examined for multicollinearity. A significance level of 5% was considered throughout and statistical analyses were performed using the R statistical package [25].

Ethics:

Ethical approval was obtained from the East Midlands National Research Ethics Service committee. All participants were provided with patient information leaflets and written consent obtained. The study was conducted in accordance with the Declaration of Helsinki and institutional good clinical practice framework.

Results:

Of 176 haemodialysis patients in two centres, 100 met the inclusion criteria; and 82 were able to complete both MOCA 1 and MOCA 2 tests. Sixty five patients agreed to have a 3rd assessment a week later (MOCA 3). Figure 1 shows the flow diagram of study samples.

Median age was 72 years (53 - 91) and 49 patients (60%) were male. Median dialysis vintage was 40 months (range: 3 - 388) and 23 patients (28%) were diabetic. Demographic and baseline characteristics are detailed in Table 1. Twenty six patients (31.7%) had asymptomatic hypotension (systolic BP drop \geq 20 mmHg) over the dialysis session. Sixty two patients (76%) had cognitive impairment before ~~/at the~~ start of HD session (MOCA score $<$ 24) with 12 (15%) having severe CI (MOCA $<$ 17).

Cognitive function of the cohort declined significantly over the course of a dialysis session (MOCA score 20.9 ± 4.9 to 19.1 ± 4.1 , $p < 0.001$, Figure 2). In 55 patients (67%) the MOCA score declined, median change -3 (range 1 to 9). In 27 patients (33%) the MOCA score remained stable or improved slightly, median change +1.5 (range 0-10) (Figure 3). Seventy-five patients (91.5%) had cognitive impairment post-haemodialysis (MOCA score $<$ 24) with 20% in severe category (MOCA $<$ 17). Most domains of cognitive function were affected namely attention, language, abstraction, and delayed recall with a very small improvement in orientation. (Table 2). There was no difference in change in MOCA score (MOCA 1 – MOCA2) between those who had MOCA1 before start of HD (median 3.5, range 13 to -15) and those who had MOCA 1 in the first half hour of start of HD (median 3, 14 to – 9). In the subgroup of patients (n=65) who had a further assessment within a week, cognitive function improved back to their initial pre-dialysis level (MOCA 1 v MOCA 3, 21.2 ± 4.5 v 21.1 ± 4.6 , $p = 0.7$).

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On univariate linear regression analysis, none of the factors studied correlated with change in the MOCA score over HD (MOCA 1 – MOCA 2) except atrial fibrillation ($p = 0.04$) although there were only 4 patients out of 82 (0.05%) had atrial fibrillation. Multiple regression model using nine potentially biologically important factors, age and dialysis vintage were independently associated with change in the MOCA score (MOCA1 – MOCA2) (Table 3).

Discussion:

In a cohort of maintenance haemodialysis patients over the age of 50, we have found a significant decline in cognitive function over a single dialysis session in majority of patients. There were deteriorations in multiple domains of cognition including attention, abstraction, delayed recall and language; there was a small but significant improvement in orientation. Age and dialysis vintage were independently associated with decline in cognitive function.

Consistent with previous observations, 76% of patients had at least mild cognitive impairment at the start of haemodialysis session, of which 15% had severe cognitive impairment. This is particularly significant given all patients known to have a diagnosis of dementia had been excluded from the study. In two thirds of patients cognition declined post-dialysis with a median decline in MOCA score of 3 (range 1 to 9; 14%). Although this may appear to be a small change, it is clinically relevant given the baseline (pre-dialysis) cognitive function was significantly below normal.

Evidence on the effect of a single haemodialysis session on cognition is contradictory. Some studies have demonstrated deterioration in cognition over a dialysis session whilst others showing improvement mostly a day or so after the dialysis session [4,16-20]. All of these studies had small sample sizes (the largest enrolling 57 patients) which might contribute to the inconsistent results. The small sample size also limited adjustment for putative risk factors [26].

The most recent and best designed of these studies used 28 stable haemodialysis patients and a control group from the community with normal kidney function. They assessed cognitive function by a battery of neuro-psychological tests before the start of a haemodialysis session and 19 hours after the end of haemodialysis demonstrating improvement in some domains of cognitive function including memory, psychomotor and executive functions [20]. Although, the authors and the accompanying editorial [26] concluded that cognitive function improved after a single haemodialysis session, this study actually did not test cognitive function immediately after a haemodialysis session. In our study, cognitive function was tested immediately before and after a haemodialysis session in a much larger cohort of patients (n=82) demonstrating significant deterioration in cognition. The improvement in cognition on further testing in a week pre-dialysis (MOCA 3) further supports the observation that the haemodialysis process causes decline in cognitive function, albeit temporary, over haemodialysis session in this cohort. The difference in results between studies, i.e. some showing improvement in cognitive function post dialysis and others showing decline, appears to be related to the timing of the post-dialysis testing; with testing immediately after dialysis session showing decline whilst testing hours or a day after showing improvement. We believe haemodynamic stress associated with haemodialysis leads to temporary deterioration in cognitive function which subsequently recovers after a few hours to show improvement in cognitive function which is related to clearance of uraemic toxins during dialysis. However, the recurrent transient cerebral insult, reflected in temporary reduction in cognitive function,

possibly contributes to longer term gradual decline in cognitive function and brain changes as discussed below.

The haemodialysis procedure causes considerable systemic circulatory stress. With loss of cerebral arterial autoregulation in these patients, it is possible that the haemodynamic stress is transmitted to the cerebral circulation with each haemodialysis session causing recurrent cerebral injury [27]. This effect on coronary circulation is now well established with intradialytic echocardiographic studies demonstrating myocardial stunning [28,29]. The reduction in cardiac contraction further reduces cerebral micro-perfusion [30]. A recent randomized controlled study elegantly showed that the use of cool dialysate (1°C below core body temperature), known to reduce haemodynamic instability during haemodialysis, abrogated the white matter changes in the brain of HD patients, providing indirect evidence for the role of recurrent cerebral microcirculatory injury associated with haemodialysis [31].

Previous studies have demonstrated correlation between fluctuations in cognitive function during haemodialysis and a number clinical and biochemical parameters [18,19,32]. In our study, there were no correlation between change in cognition over HD and any of these factors on univariate analysis. [We also didn't find correlation between change in cognition and intra-dialytic hypotension, dialysis blood flow rate, dialysate flow rate, ultrafiltration volume, or history of congestive cardiac failure.](#) However, multiple regression using nine potentially biologically important factors in the model showed, age and the length of time the patient had been on haemodialysis treatment were independently associated with change in cognition over dialysis. Depression, common in haemodialysis patients and known to be associated with impaired cognitive function tests [33,34], was also not associated with change in cognitive function. Cognitive function starts declining in middle life and progresses with age [35]. The association with decline over a dialysis session perhaps suggests increased susceptibility to the haemodynamic changes related to haemodialysis with aging. On the other hand, the association with dialysis vintage may indicate repetitive ischaemic-reperfusion injury associated with the haemodialysis process [13] may have a role in cognitive decline.

Structural magnetic resonance imaging (MRI) studies of the brain in haemodialysis patients showed a preponderance of white matter changes in the form of infarcts, micro-bleeds and diffuse changes white matter termed leukoaraiosis [15,36-43]. The cerebral white matter

structural changes are particularly relevant because of their association with fluctuations in cognitive performance [443] as demonstrated in our study. Functional magnetic resonance imaging studies (fMRI) showed reduced regional homogeneity in bilateral frontal, parietal and temporal regions of the brain in patients with end-stage kidney disease which correlated with cognitive function tests. These changes were more prominent in haemodialysis patients compared to non-dialysed end-stage kidney disease patients and correlated with cognitive impairment, pre-dialysis serum creatinine and duration of haemodialysis [45-465]. Another fMRI study of whole brain in haemodialysis patients showed bilateral activation of hippocampus suggesting activation of memory-relevant brain areas during dialysis [476]. These conclusions suggest that the haemodialysis process may have a role in cognitive impairment.

Retention of uraemic toxins which are incompletely cleared by haemodialysis may also be responsible for chronic cognitive impairment [11,12]. There are more than 200 uraemic metabolites most which have unknown effect on cerebral function and clearance by dialysis. A recent metabolomic study has identified four uraemic metabolites (4-hydroxyphenylacetate, phenylacetylglutamine, hippurate, and prolyl-hydroxyproline) which were independently associated with impairment of cognitive function [487].

The results of this study have significant clinical implications. The deterioration in cognitive function over a haemodialysis session is associated with impaired capacity to actively process and retain information; this in turn is likely to be associated with impaired health literacy and ability to perform health related tasks. For example, poor adherence to dietary and medication advice given during dialysis could be related to this. As such, reviewing patients and giving advice whilst they are undergoing haemodialysis, a common practice in many parts of the world, may not be advisable especially towards the latter half of a dialysis session and in those showing significant cognitive function decline over haemodialysis. Decline in cognition over a haemodialysis session can also affect performance of tasks such as driving and other practical skills. It may also affect their capacity to take important decisions or signing important documents, like advance directives, during or immediately after haemodialysis. One may argue, on the basis of these findings, haemodialysis patients should have cognitive function tested periodically, pre and post dialysis, to inform their capacity to undertake tasks, such as driving after dialysis. Further research is needed to address this important issue.

This study has a number of limitations, the most important of which being the relatively small sample size although this study is a bigger cohort than any other study assessing change in cognitive function over a dialysis session published to date. Secondly, this study used MOCA tool to assess cognitive function. Using a battery of neuro-psychological tests would have made the results more robust. The rationale for using MOCA is described in the next paragraph. Thirdly, executive function was not examined separately as has been done in some previous studies looking at cognitive function in haemodialysis patients at a single time point²⁷. Fourthly, a MOCA test before the next dialysis showing improvement in cognition would support our observations further. However, we were unable to perform this owing to logistical reasons. Equally, knowing the MOCA score, before the patient joined the haemodialysis programme, would provide a true baseline cognitive function. Lastly, this study did not include a control group for it is difficult to choose an appropriate reference group for an observational study involving haemodialysis patients [21]. Healthy individuals or those with chronic kidney disease not requiring dialysis cannot be subjected to the dialysis procedure for ethical reasons. Peritoneal dialysis patients could be used, but it would be a comparison of two different dialysis modalities. Although having haemodialysis patients sit for 4 hours without dialysis on the day of their scheduled dialysis may have provided control, it is debatable whether this would be ethically justifiable.

The rationale for using the MOCA to assess cognitive function are as follows: 1) The MOCA has been validated in haemodialysis patients against a battery of neuropsychological tests covering the domains of memory, attention, language, visuospatial and executive functions [22]. 2) It is more sensitive than the Mini Mental State Examination the most commonly used screening test [22]. 3) It is of suitable length and takes only 10 minutes to administer. 4) It is freely available. 5) There are 3 parallel versions available which help to avoid learning effect when cognitive tests are repeated over a short period of time (e.g. before and after a haemodialysis session). 6) The MOCA assesses cognitive impairment in 8 domains namely visuo-spatial/ executive, memory, naming, delayed recall, orientation, attention, abstraction and language functions. 7) It has defined cut scores for clinical cognitive impairment in haemodialysis patients [22] and 8) MOCA is adjusted for educational level (+1 for ≤ 12 year of education). All these attributes make MOCA a suitable tool for implementation for routine cognitive function assessment in the haemodialysis unit in the future.

The main strength of our work is that it systematically examined the change in cognitive function over a haemodialysis session and determined its association with an extensive set of covariates related to kidney disease and dialysis that represent important controls via exclusion or statistical adjustment, and might potentially be used to determine why performance declines after a dialysis session. This has never been done before within a single study. Association of change in cognition with educational status was not assessed separately as the MOCA is adjusted for education level, and also cognition was compared before and after dialysis in the same subjects.

We have demonstrated that there is a significant decline in cognitive function over a haemodialysis session involving many domains with age and dialysis vintage being independently associated with this decline. The results of this study raise a number of questions. What causes this decline in cognitive function over a haemodialysis session? Is it related to haemodynamic stress, ischaemic reperfusion injury, in the background of impaired cerebral auto-regulation; or is it due to neuro-chemical imbalance associated with accumulation uraemic neuro-toxins? Is recurrent ‘cerebral insult’, associated with each session of haemodialysis responsible for the more severe and rapidly progressive cognitive impairment observed in these patients? And finally, what can we do to help prevent acute and the progressive decline in cognition in haemodialysis patients? There is need for further work to answer these questions.

References:

1. Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol* 2005;16:2127-33.
2. Davey A, Elias MF, Robbins MA, Seliger SL, Dore GA. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2013;28:1810-9.
3. Sedaghat S, Vernooij MW, Loehrer E, Mattace-Raso FUS, Hofman A, van der Lugt A, et al. Kidney Function and Cerebral Blood Flow: The Rotterdam Study. *Journal of the American Society of Nephrology* 2015.
4. Griva K, Stygal J, Hankins M, Davenport A, Harrison M, Newman SP. Cognitive Impairment and 7-Year Mortality in Dialysis Patients. *American Journal of Kidney Diseases* 2010;56:693-703.
5. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al. Cognitive impairment in hemodialysis patients is common. *Neurology* 2006;67:216-23.
6. Schneider SM, Kielstein JT, Braverman J, Novak M. Cognitive Function in Patients With Chronic Kidney Disease: Challenges in Neuropsychological Assessments. *Seminars in nephrology* 2015;35:304-10.
7. O'Lone E, Connors M, Masson P, Wu S4, Kelly PJ, Gillespie D, Parker D, Whiteley W, Strippoli GF, Palmer SC, Craig JC, Webster AC1. Cognition in People With End-Stage Kidney Disease Treated With Hemodialysis: A Systematic Review and Meta-analysis. *Am J Kidney Dis.* 2016 Jun;67(6):925-35. doi: 10.1053/j.ajkd.2015.12.028. Epub 2016 Feb 23.
8. Drew DA, Weiner DE. Cognitive impairment in chronic kidney disease: keep vascular disease in mind. *Kidney international* 2014;85:505-7.
9. Miwa K, Tanaka M, Okazaki S, Furukado S, Yagita Y, Sakaguchi M. et al. Chronic kidney disease is associated with dementia independent of cerebral small-vessel disease. *Neurology* 2014;82:1051-7.
10. Lu R, Kiernan MC, Murray A, Rosner MH, Ronco C. Kidney-brain crosstalk in the acute and chronic setting. *Nature Reviews Nephrology* 2015;11:707-19.
11. Lisowska-Myjak B. Uremic toxins and their effects on multiple organ systems. *Nephron Clinical practice* 2014;128:303-11.
12. Kielstein H, Suntharalingam M, Perthel R, Song R, Schneider SM, Martens-Lobenhoffer J, et al. Role of the endogenous nitric oxide inhibitor asymmetric dimethylarginine (ADMA) and brain-derived neurotrophic factor (BDNF) in depression and behavioural changes: clinical and preclinical data in chronic kidney disease. *Nephrol Dial Transplant* 2015;30:1699-705.
13. Odudu A, McIntyre C. Influence of dialysis therapies in the development of cardiac disease in CKD. *J Ren Care* 2010;36 Suppl 1:47-53.
14. Dubin RF, Teerlink JR, Schiller NB, Alokzai D, Peralta CA, Johansen KL. Association of segmental wall motion abnormalities occurring during hemodialysis with post-dialysis fatigue. *Nephrol Dial Transplant* 2013;28:2580-5.
15. Prohovnik I, Post J, Uribarri J, Lee H, Sandu O, Langhoff E. Cerebrovascular effects of hemodialysis in chronic kidney disease. *Journal of Cerebral Blood Flow and Metabolism* 2007;27:1861-9.

16. Murray AM, Pederson SL, Tupper DE, Hochhalter AK, Miller WA, Li Q et al. Acute variation in cognitive function in hemodialysis patients: a cohort study with repeated measures. *Am J Kidney Dis* 2007;50:270-8.
17. Williams MA, Sklar AH, Burright RG, Donovan PJ. Temporal effects of dialysis on cognitive functioning in patients with ESRD. *Am J Kidney Dis*. 2004 Apr;43(4):705-11.
18. Griva K, Newman SP, Harrison MJ, Hankins M, Davenport A, Hansraj S et al. Acute neuropsychological changes in hemodialysis and peritoneal dialysis patients. *Health Psychol*. 2003;22(6):570-578.
19. Costa AS, Tiffin-Richards FE, Holschbach B, Frank RD, Vassiliadou A, Krüger T, Eitner F, Gross T, Shah NJ, Schulz JB, Floege J, Reetz K. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. *Am J Kidney Dis*. 2014 Sep;64(3):434-42. doi: 10.1053/j.ajkd.2014.02.012. Epub 2014 Mar 27.
20. Schneider SM, Malecki AK, Müller K, Schönfeld R, Girndt M, Mohr P, Hiss M, Kielstein H, Jäger K, Kielstein JT. Effect of a single dialysis session on cognitive function in CKD5D patients: a prospective clinical study. *Nephrol Dial Transplant*. 2015 Sep;30(9):1551-9. doi: 10.1093/ndt/gfv213. Epub 2015 Jun 11.
21. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005; 53(4):695-9.
22. Tiffin-Richards FE, Costa AS, Holschbach B, Frank RD, Vassiliadou A, Krüger T, Kuckuck K, Gross T, Eitner F, Floege J, Schulz JB, Reetz K. The Montreal Cognitive Assessment (MoCA) - a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. *PLoS One*. 2014 Oct 27;9(10):e106700. doi: 10.1371/journal.pone.0106700.
23. Greenberg SA. 2007. How to Try This: The Geriatric Depression Scale: Short Form. *Am J Nurs*; 107(10): 60-69
24. Inouye SK, van Dyck S, Alessi C, Balkin C, Siegel AP, Horwitz RI. 1990. Clarifying confusion: the confusion assessment method. *Ann Intern Med*; 113(12): 941-948.
25. R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.
26. Elias MF, Seliger SL, Torres RV; Improved cognitive performance after a single dialysis session: where do we go from here?. *Nephrol Dial Transplant* 2015; 30 (9): 1414-1417. doi: 10.1093/ndt/gfv263
27. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; 4: 914–920.
28. Odudu A, Eldehni MT, McCann GP, McIntyre CW. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clin J Am Soc Nephrol*. 2015 Aug 7;10(8):1408-17.
29. McIntyre CW and Goldsmith DJ. Ischemic brain injury in hemodialysis patients: which is more dangerous, hypertension or intradialytic hypotension? *Kidney International* (2015) 87, 1109–1115.
30. Eldehni MT, McIntyre CW. Are there neurological consequences of recurrent intradialytic hypotension? *Semin Dial* 2012; 25: 253–256

31. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol*. 2015 Apr;26(4):957-65. doi: 10.1681/ASN.2013101086. Epub 2014 Sep 18.
32. Sarnak MJ, Tighiouart H, Scott TM, Lou KV, Sorensen EP, Giang LM, Drew DA, Shaffi K, Strom JA, Singh AK, Weiner DE. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. *Neurology*. 2013 Jan 29;80(5):471-80. doi: 10.1212/WNL.0b013e31827f0f7f
33. Kurella Tamura M, Larive B, Unruh ML, Stokes JB, Nissenson A, Mehta RL, Chertow GM; Frequent Hemodialysis Network Trial Group. Prevalence and correlates of cognitive impairment in hemodialysis patients: the Frequent Hemodialysis Network trials. *Clin J Am Soc Nephrol*. 2010 Aug;5(8):1429-38. doi: 10.2215/CJN.01090210. Epub 2010 Jun 24.
34. Agganis BT, Weiner DE, Giang LM, Scott T, Tighiouart H, Griffith JL, Sarnak MJ. Depression and cognitive function in maintenance hemodialysis patients. *Am J Kidney Dis*. 2010 Oct;56(4):704-12. doi: 10.1053/j.ajkd.2010.04.018. Epub 2010 Jul 29.
35. Balogun RA, Balogun SA, Kepple AL, Ma JZ, Turgut F, Kovesdy CP, Abdel-Rahman EM. The 15-item geriatric depression scale as a predictor of mortality in older adults undergoing hemodialysis. *J Am Geriatr Soc*. 2011 Aug;59(8):1563-5. doi: 10.1111/j.1532-5415.2011.03533.x.
36. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009 Apr; 30(4): 507–514. Nakatani T, Naganuma T, Uchida J et al. Silent cerebral infarction in hemodialysis patients. *Am J Nephrol* 2003;23: 86–90.
37. Nakatani T, Naganuma T, Uchida J, et al. Silent cerebral infarction in hemodialysis patients. *Am J Nephrol*. 2003 Mar-Apr;23(2):86-90.
38. Anan F, Shimomura T, Imagawa M, Masaki T, Nawata T, Takahashi N et al. Predictors of silent infarction in patients with chronic renal failure undergoing hemodialysis. *Metabolism* 2007; 56: 593–598.
39. Anan F, Shimomura T, Kaku T, Kaneda K, Imagawa M, Tsukagawa H, et al. High-sensitivity C-reactive protein level is a significant risk factor for silent cerebral infarction in patients on hemodialysis. *Metabolism* 2008; 57: 66–70.
40. Kamata T, Hishida A, Takita T, Sawada K, Ikegaya N, Maruyama Y, et al. Morphologic abnormalities in the brain of chronically hemodialyzed patients without cerebrovascular disease. *Am J Nephrol* 2000; 20: 27–31.
41. Lamar M, Catani M, Price CC, Heilman KM, Libon DJ. The Impact of region-specific Leukoaraiosis on working memory deficit in dementia. *Neuropsychologia* 2008; 46: 2597–2601.
42. Onen F, Henry-Feugeas MC, Roy C, Baron G, Ravaud P. Mobility decline of unknown origin in mild cognitive impairment: an MRI-based clinical study of the pathogenesis. *Brain Res* 2008; 1222: 79–68.
43. Kim CD, Lee HJ, Kim DJ, Kim BS, Shin SK, Do JY, et al. High prevalence of leukoaraiosis in cerebral magnetic resonance images of patients on peritoneal dialysis. *Am J Kidney Dis* 2007;50: 98–107.
44. Fjell AM, Westlye LT, Amlie IK, Walhovd KB. Reduced white matter integrity is related to cognitive instability. *J Neurosci*. 2011;31(49):18060-18072.
45. Chen HJ, Qi R, Kong X, Wen J, Liang X, Zhang Z, Li X, Lu GM, Zhang LJ. The impact of hemodialysis on cognitive dysfunction in patients with end-stage renal disease: a resting-state functional MRI study. *Metab Brain Dis*. 2015 Oct;30(5):1247-56. doi: 10.1007/s11011-015-9702-0.

46. Zhang XD, Wen JQ, Xu Q, Qi R, Chen HJ, Kong X, Wei LD, Xu M, Zhang LJ, Lu GM. Altered long- and short-range functional connectivity in the patients with end-stage renal disease: a resting-state functional MRI study. *Metab Brain Dis.* 2015 Oct;30(5):1175-86. doi: 10.1007/s11011-015-9683-z.
47. Lux S, Mirzazade S, Kuzmanovic B, Plewan T, Eickhoff SB, Shah NJ, Floege J, Fink GR, Eitner F. Differential activation of memory-relevant brain regions during a dialysis cycle. *Kidney Int.* 2010 Oct;78(8):794-802
48. Kurella Tamura M, Chertow GM, Depner TA, Nissenson AR, Schiller B, Mehta RL, Liu S, Sirich TL; FHN Study. Metabolic Profiling of Impaired Cognitive Function in Patients Receiving Dialysis. *J Am Soc Nephrol.* 2016 Jul 21. pii: ASN.2016010039.

Legends for figures:

Figure 1: Flow diagram for the study sample

Figure 2: Change in cognitive functions before and after a [single](#) haemodialysis session and before dialysis one week after

Figure 3: Line charts of changes in cognitive functions over a haemodialysis session in individual patients

Table 1: Demographic and other characteristics of the cohort (n=82)

Characteristic	Value
Age (years, median and range,)	73 (53 – 91)
Sex (male, %)	59 (72%)
Diabetes (%)	28 (34%)
Non-smoker (%)	90
Dialysis vintage (months, median and range)	40.5 (3 – 88)
Geriatric Depression Score (mean, SD)	4.9 (3.1)
Charlson Score (mean, SD)	2.6 (1.9)
Cerebrovascular disease (%)	9
Use of psychoactive drugs (%)	40
KT/V (mean and SD)	1.5 (0.3)
Pre-dialysis BP (mmHg, mean and SD)	142/67 (21/15)
Post-dialysis BP (mmHg, mean and SD)	130/62 (22/12)
Pre-dialysis body weight (Kg, median and range)	75.8 (44.9 – 126.5)
Post-dialysis body weight (Kg, median and range)	72.5 (44.2 – 115.4)
Change in intra-dialytic systolic BP (mmHg, mean and SD)	11.9 (25.7)
Blood flow rate (ml/min, mean and SD)	338.8 (56.6)
Ultrafiltration volume (Litre, median and range)	1.5 (-0.5 – 3.6)
Haemoglobin (gm/L, mean and SD)	115 (15)
Serum sodium (mmol/L, mean and SD)	136.3 (2.5)
Serum potassium (mmol/L, mean and SD)	4.7 (0.8)
Serum calcium (mmol/L, mean and SD)	2.3 (0.2)
Serum phosphate (mmol/L, mean and SD)	1.5 (0.4)
Serum albumin (gm/L, mean and SD)	31.3 (4.2)
Serum bicarbonate (mmol/L, mean and SD)	23.4 (2.7)

BP – blood pressure

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Table 2: Summary statistics for cognitive function scores before and after HD session.

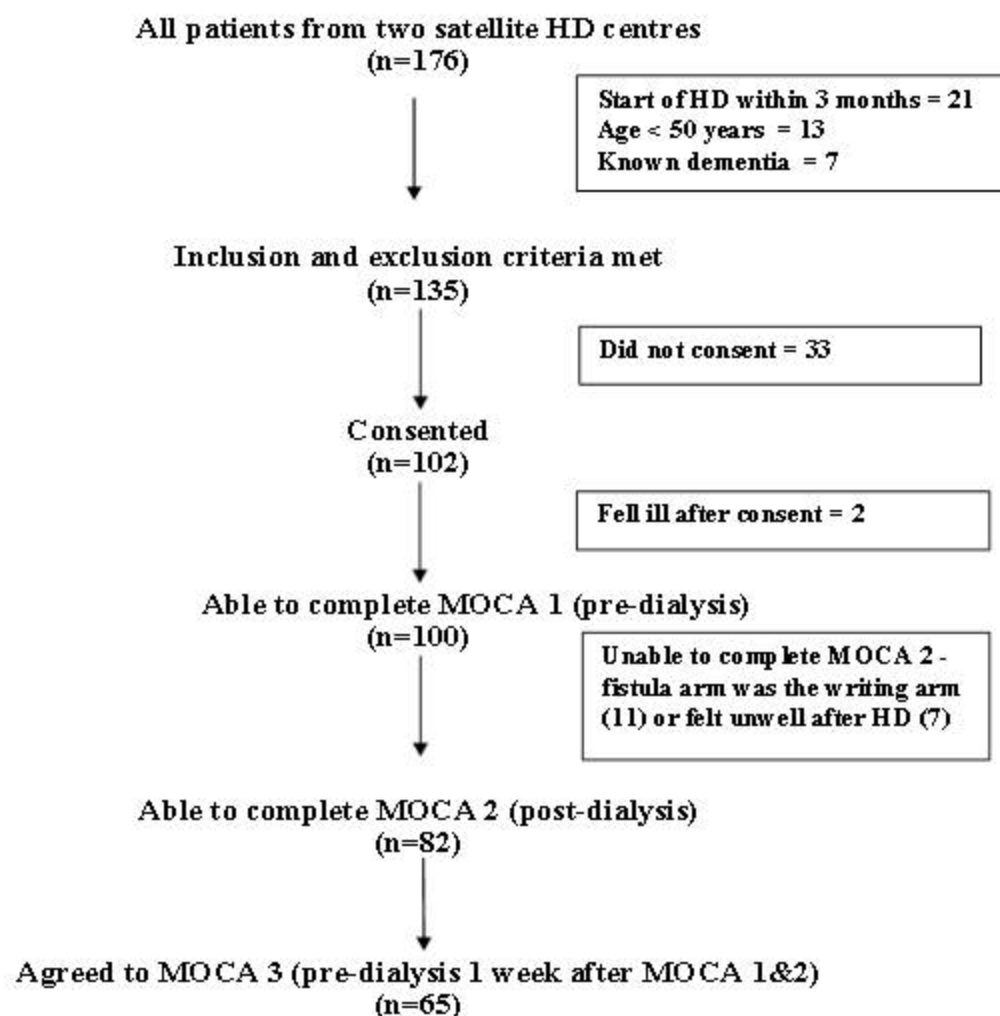
Outcome	Before HD session		After HD session		P-value
	Mean (SD)	Median (25 th , 75 th percentile)	Mean (SD)	Median (25 th , 75 th percentile)	
MOCA	21 (4.8)	21 (19, 24)	19.1 (4.1)	19 (17, 22)	<0.001
Visuo-spatial	2.8 (1.4)	3 (2, 4)	2.8 (1.4)	3 (2, 4)	0.98
Naming	2.8 (0.5)	3 (3, 3)	2.8 (0.5)	3 (3, 3)	0.66
Attention	4.8 (1.4)	5 (4, 6)	4.6 (1.3)	5 (4, 6)	0.05
Language	1.6 (1)	2 (1, 2)	1 (0.9)	1 (0, 2)	<0.001
Abstraction	1.3 (0.8)	1 (1, 2)	1 (0.8)	1 (0, 2)	0.001
Delayed recall	2.2 (1.6)	2 (1, 4)	1.2 (1.4)	1 (0, 2)	<0.001
Orientation	5.5 (0.7)	6 (5, 6)	5.7 (0.7)	6 (6, 6)	0.004

Table 3: Multiple regression analyses with regression coefficients (95% CI) for selected biologically important risk factors and change in MOCA score.

Variable	Beta coefficient (95% CI)	P-value
Age (years)	-0.09 (-0.17, -0.01)	0.04*
Sex (Ref=Female)	-0.83 (-2.47, 0.81)	0.32
Dialysis vintage (months)	-0.02 (-0.04, -0.002)	0.03*
Geriatric depression score	-0.18 (-0.47, 0.11)	0.22
Charlson score	-0.13 (-0.6, 0.33)	0.57
Cerebrovascular disease (Ref=No)	1.13 (-1.69, 3.95)	0.43
Sedating drugs (Ref=No)	1.14 (-0.47, 2.75)	0.16
Change in blood pressure (mmHg)	-0.02 (-0.05, 0.01)	0.2
Change in weight (Kg)	-0.52 (-1.31, 0.27)	0.19

SBP – systolic blood pressure, GDS – Geriatric depression Scale, *statistically significant

Figure 1: Flow diagram for the study sample



HD – haemodialysis, MOCA – Montreal Cognitive Assessment (1 before HD, 2 after HD, 3 one week after)

MOCA score

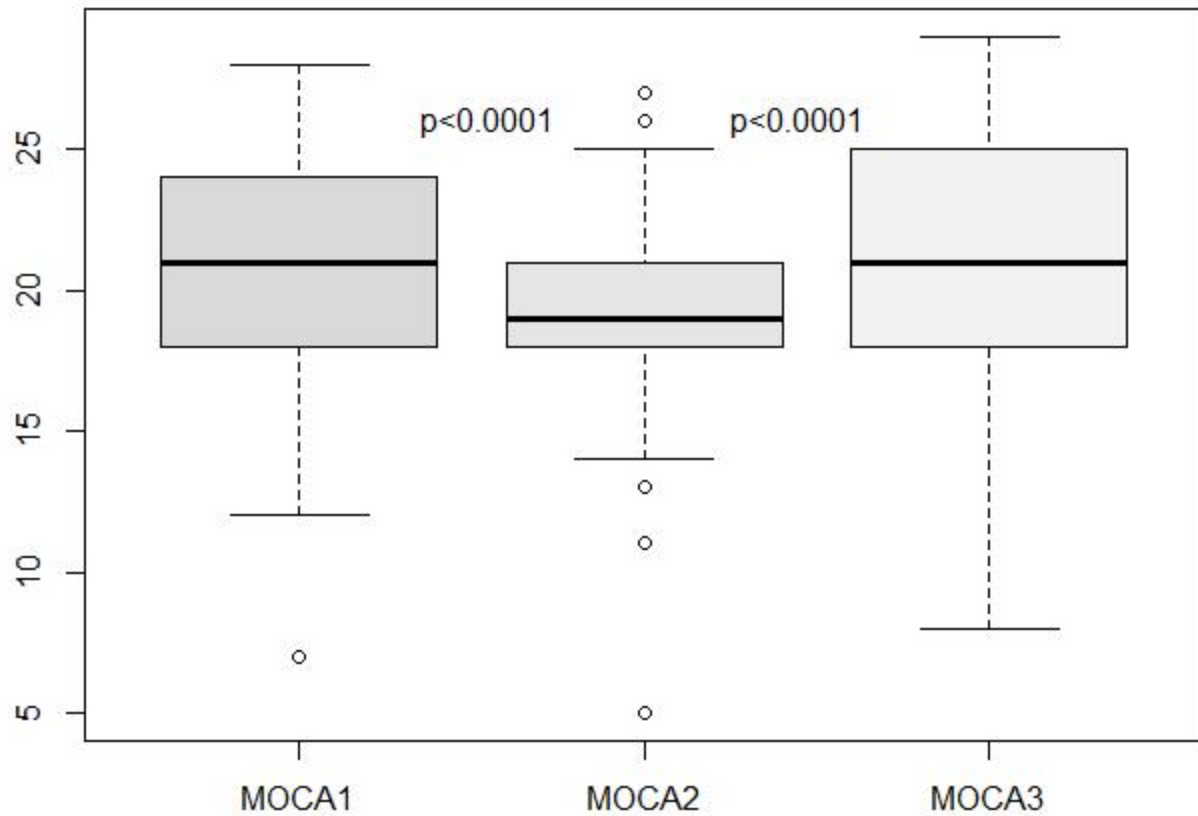
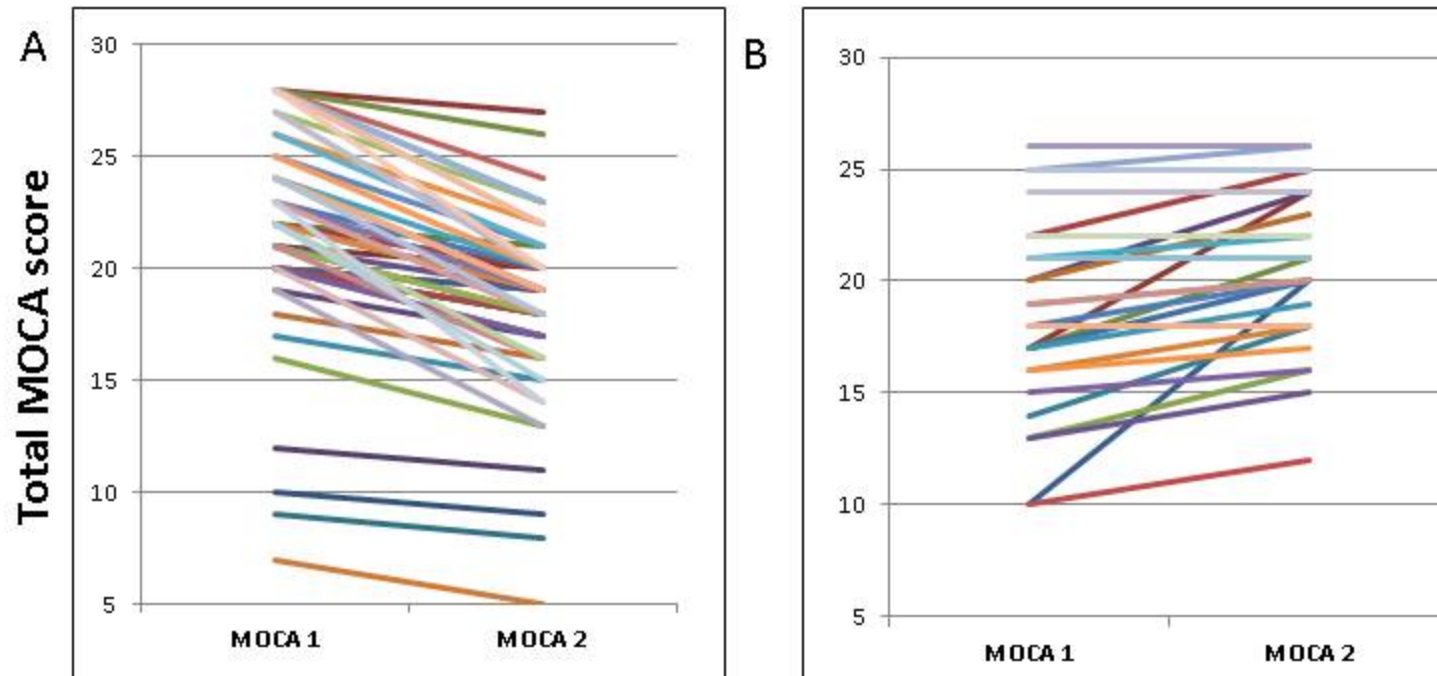


Figure 3: Line charts of change in cognitive function over a haemodialysis session



Change in MOCA score from pre to post haemodialysis session: A) Decliners (n=55, 67%) – median change -3 (range: 1 – 9) B) Stable (n=27, 33%) – median change +1.5 (range: 0-10)