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Risk and incidence of cognitive impairment in patients with chronic kidney disease and diabetes: the results from a longitudinal study in a community cohort of patients and an age and gender-matched control cohort in North Wales, UK

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ABSTRACT

Objectives The aim of the current investigation is to estimate the incidence and risk for neurocognitive disorders (NCD) in a chronic kidney disease (CKD) cohort with diabetes, compared with an age and sex-matched control cohort.

Design Longitudinal follow-up.

Setting District general hospital North Wales, UK.

Participants Ninety-two patients with CKD and an age and gender-matched sample of 143 controls at baseline and at approximately 36 months.

Interventions Cognitive function was assessed in the patients with CKD (mean age 75.8±9.1; 49 men: 43 women) and the control cohort (mean age 74.4±6.2; 71 men: 72) at baseline and at approximately 36 months. An NCD diagnosis was based on patient, informant, case note review, neuropsychological assessment and application of Diagnostic and Statistical Manual of Mental disorders V.5 (DSM-5) for an NCD and Petersen's criteria for mild cognitive impairment.

Results Follow-up neuropsychological assessment and application of DSM-5 criteria of the cognitively normal patients and controls revealed, 25/92 (27%) of the CDK and 20/143 (13.9%) in the control cohort developed an NCD. The CKD cohort had a twofold increased risk for the development of an NCD compared with the controls, adjusted for age and sex. The incidence rate for an NCD in the CKD cohort was 10.5 and 5.1 in the controls, respectively. No association was observed with the stage of CKD and cognitive function.

Conclusions This longitudinal investigation found that patients with CKD have a twofold increased risk for the development of an NCD. The current investigation highlighted the need to recognise that NCD in patients with CKD is a common comorbidity and that they are at a much higher risk for the development of a significant neurodegenerative disorders. In view of these risks, neuropsychological screening and assessment should be incorporated into normal CKD clinical practice and management.

Strengths and limitations of this study

- ► This is the first UK study to investigate the risk and incidence of neurocognitive disorders in patients with mild to moderate chronic kidney disease and diabetes.
- ► The study adopted a longitudinal design with an age and gender-matched control group.
- ► All patients' and controls cognitive function was formally evaluated by neuropsychological assessment and application of Diagnostic and Statistical Manual of Mental Disorders V.5 criteria.
- ► The limitation of this study is the absence of neuroimaging to confirm or support cardiovascular diagnosis.

BACKGROUND

Chronic kidney disease (CKD) is a global healthcare condition associated with several comorbid conditions including, cardiovascular disease, hypertension (HT) and type 2 diabetes mellitus (T2DM).[1] With reference to non-communicable diseases, CKD has been reported to be the 16th leading cause of mortality worldwide.[2] For people living with CKD, there is the additional increased risk of developing other comorbid diseases, which will inevitably contribute to what has been described as the years of life lost or premature death. Although mortality rates in many of the leading causes of death are believed to be stabilising, or declining, the consequence of this is that many people will live longer with multiple comorbid debilitating conditions. This will undoubtedly impact on the clinical management of chronic conditions such as CKD, where

more focused primary and secondary prevention aimed at earlier assessment and intervention is needed.[3] This can be achieved through the careful setting and implementation of public health priorities that can ensure patients receive optimal care and management of their condition, which can lead to improvements in their overall health and well-being.[4] Given that CKD is a systemic condition, its relation with neurological function warrants closer investigation, especially in view of the increase in the prevalence of CKD in ageing populations.[5] The relationship between the brain and CKD is important to consider because these physical structures are vulnerable to vascular and haemodynamic changes, which can present in the patients with CKD as neurodegenerative dysfunction such as mild cognitive impairment (MCI) or dementia, which are often for a number of reasons overlooked in the clinical management of CKD.[6]

Worldwide prevalence rates for dementia suggest there are at least 50 million people living with this condition, with projections by the midpoint of this century indicating that the estimated number of cases will rise to over 130 million.[7] While it is recognised that cognitive impairment in CKD, compared with general population, appears to occur more frequently at all stages of the condition, its aetiology is as yet to be fully determined.[8–10] In view of the known adverse outcomes associated with cognitive impairment, which include disability, increased risk of acute hospital admissions, reduced quality of life, carer strain, impaired decision-making and increased risk for mortality, it is important that patients with CKD are screened routinely. Together with this, there is also a need to establish more robust prevalence and incidence estimates, to ensure that clinical teams and policymakers incorporate them into their current and future healthcare planning and provision.

Previously in a cohort of patients with CKD with concomitant T2DM, we reported the prevalence of neurocognitive disorders (NCD) ranging from mild impairment to dementia to be around 48%.[11] The recent study from the longitudinal Brain In Kidney disease study group also reported comparable prevalence figures for cognitive impairment in their cohort of patients with advanced CKD.[12] However, both these studies are at risk of overinterpretation because they included existing cases of cognitive impairment at baseline, possibly skewing the prevalence rates. To address these concerns, this follow-up study will report the incidence and risk for NCD, ranging from mild to major impairment in our CKD cohort, compared with an age and sex-matched control cohort, who at baseline were considered to have normal cognitive function. This study will also investigate if the progression of CKD severity is independently associated with NCD. In addition, baseline measures including demographic, clinical measures including several blood and urine biomarkers routinely measured in CKD, along with mood, and quality of life will be explored to test for associations with cognitive function.

METHODS

Cohort inclusion criteria

The inclusion criteria for both cohorts included no previous history of an existing diagnosis of an NCD, including Alzheimer's disease (AD), vascular dementia, other dementing or other neurological condition. In addition, subjects were excluded if they had previously had a transient ischaemic attack, stroke or had severe sensory impairment, a significant head injury, a history of alcohol or recreational drug misuse or significant neuropsychiatric disturbance. The CKD cohort did not include patients if they were at the end stage of their kidney disease (estimated glomerular filtration rates; eGFR <15 mL/min/1.73 m^2), in receipt of renal replacement therapy or were a transplant recipient. Likewise, the control cohort excluded subjects with an existing diagnosis of CKD (eGFR >60 mL/min/1.73 m^2) or T2DM.

CKD cohort

The baseline CKD cohort assembly, along with their cognitive and physical assessments, is described in greater detail elsewhere.[11] Briefly, 178 participants (97 men: 81 women) aged 55 years and over with an established diagnosis of CKD with an eGFR (eGFR based on MDRD equation) of <60 mL/min/1.73 m^2 and a confirmed diagnosis T2DM were initially recruited into the study. At baseline, 86/178 (48%) of the cohort had an NCD and are excluded from the analysis in the current study, leaving 92 patients at baseline with normal cognitive function.

Control cohort

A representative control cohort matched for age (±3 years) and gender was recruited from local general practices in the same geographical region of North Wales, UK, from which the CKD cohort was drawn. A total of 222 control subjects were invited to participate in the study, of which 32 declined participation, a further six were excluded because four were found to have a diagnosis of CKD and two had T2DM. On baseline cognitive assessment, 22 fulfilled criteria for MCI and 11 for dementia, leaving a cohort of 149 controls with normal cognitive function at baseline included in the current study. All participants in this study were assessed in-person and contacted by telephone between clinical assessments, until approximately 36 months postbaseline assessment. The recruitment and follow-up of the cohorts are given in online supplemental figure 1.

Cognitive assessment and diagnosis of cognitive impairment

Global cognitive function of participants was assessed with the Addenbrooke's Cognitive Examination III (ACE III).[13] This instrument comprises five cognitive domains, which are summed to give individual cognitive domain and a global assessment score. Executive function was assessed with the Weigl Colour Form Sorting

Test (WCFST) and by parts A and B of the trail making tests (TMT).[14 15] The WCFST is a sorting and set shifting test and the TMT tests A and B measure attention, visuospatial scanning, motor speed and set shifting. The confirmation of an NCD diagnosis was reached through information provided by subjects, informants, clinical specialist consensus by review of medical and personal histories, neuropsychological assessment, blood, glucose and urine tests, brain imaging where available and the application of Diagnostic and Statistical Manual of Mental disorders V.5 (DSM-5).[16] This is met where individuals present with significant deficits in one or several cognitive domains that cannot be explained by delirium, or another underlying mental or physical disorder. The diagnosis for single and multiple domain MCI was reached by employing Peterson's criteria and DSM-5 criteria for mild NCD.[17 18] The diagnostic work-up for MCI NCD was established through neuropsychological assessment, reports subjects, caregivers or other informants and clinician review of symptoms of memory impairment, decline in the ability to perform everyday activities (though still able to perform these activities without assistance) and difficulties with language, perceptual-motor and social skills. Those individuals in the current study who met DSM-5 criteria for either a mild or a moderate NCD were signposted to appropriate memory and clinical pathways as appropriate.

CKD staging, blood and biomarkers

The stage of CKD was defined by the application of the Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines, where mild CKD was defined as eGFR 45 to <60, moderate stage as an eGFR of 30 to <45 and severe as an eGFR <30 µmol/L → mL/min/1.73m2.[19] In addition, demographic details, onset and duration of CKD, T2DM and HT, ischaemic heart disease (IHD), cholesterol (non-high-density lipoproteins (HDL)/HDL, low-density lipoprotein), several blood and urine biomarkers routinely measured in CKD, blood pressure, mood disorder (Patient Health Questionnaire-9) and health related quality of life (EQ-5D) were recorded.[20 21] Anaemia was defined using the WHO guidelines as haemoglobin in men <130 g/L and <120 g/L in women.[22]

Patient and public involvement

Patients and controls were not involved in the design, or conduct of the study, but were given the opportunity to comment on the results and dissemination plans of our research

Statistical analysis

The participants' demographic characteristics along with their neuropsychological assessments were summarised with descriptive statistics including ratios, mean, SD (±), median statistics and 95% CIs. To test for normality of the distribution, the data were inspected by employing the Shapiro Wilk test and Levene's test. In addition, the strength of linear association between variables was calculated with Spearman correlation coefficients. Analysis of variance (adjusted for multiple comparisons with Tukey's honesty significance test) or Kruskal-Wallis (for skewed data), explored individual cohort demographic characteristics between the stages of stages of CKD. For normally distributed continuous variables, independent t tests were employed, and for categorical variables, unadjusted χ^2 tests were used. In the case of skewed data, non-parametric Mann-Whitney U analysis was used where appropriate. The main outcomes in the current investigation were the incidence of new cases of NCD (MCI or dementia), coded to DSM-5 criteria and the eGFR KDIGO staging. The prevalence of NCD was calculated as the proportion of the cohort who were classified as a case at a given point in time. The incidence of new cases of NCD was calculated by dividing new cases by the person-time at risk throughout the observation period. The precise time a subject becomes a case is not possible to precisely know; therefore, in this study, it was assumed to occur in the midpoint of the period of observation. The relative risk (RR) and 95% CI were calculated according to theAltman method.[23]

The NCD and CKD outcome covariates were adjusted by demographics (age, education, gender), chronic conditions, including, IHD, HT, mood, blood pressure (systolic/diastolic), haemoglobin A1c and lipoprotein results. In addition, the covariates of kidney function, eGFR, creatinine and urine–albumin-creatinine (UACR) ratios were adjusted for in the statistical modelling. To examine the associations between NCD and specific cognitive domains, regression analysis was performed employing linear and binary logistic modelling where appropriate. In addition, generalised linear modelling (GLM) was also employed to test for difference in the adjusted models. SPSS V.22 software was used for all of the statistical analyses.[24] The level of significance was set at the alpha level of p<0.05.

RESULTS

At baseline, 92 CKD and 149 controls without NCD were included in this study (mean age of 74.8±7.4; 120 men: 115 women). The mean length of time for follow-up for the cohorts was 32.6 months (±7.03). There were no withdrawals, lost to follow-up or deaths in the CKD cohort during the period of observation. On follow-up of the control cohort, two died before follow-up assessment and a further four withdrew consent, leaving 143 controls included in the control group analysis. The duration of renal disease in the CKD cohort was 7.25 years (±2.61; median=7), and the duration of diabetes was 19.48 years (±9.07). The overall mean eGFR (<60 mL/min/1.73 m^2) for the CKD cohort was 28.37±12.1 (median=30), with no gender differences being observed (p=0.05). The CKD and control cohort descriptive demographics, clinical and cognitive assessment outcomes are shown in table 1.

The cumulative incidence in the CKD cohort of new cases of NCD of any type at follow-up was 25/92 (27.2%)

Table 1 A comparison between the CKD (n=92) and control (n =143) cohorts, demographic, clinical, and cognitive assessment outcomes (Mean ± SD, ratios)

	Controls (n=143)	G3* (n=48)	G4+5* (n=44)	P value†
Age	74.4±6.2	75.3±9.3	75.9±9.3	0.12‡
Gender (male: female ratio)	71:72	25:23	24:20	0.72¶
Education years	11.1 (1.8)§	11.1 (2.1)**	10.6 (1.5)**	0.007‡
EQ-5D	0.67 (0.19)§	0.55 (0.2)**	0.53 (0.24)**	0.03‡
EQ-5D (visual analogue scale %)	69.9 (14.3)§	63.8 (13.7)**	50.1 (16.4)**	0.04‡
PHQ-9	2.5 (0.75)	3.8 (1.7)	4.1 (2.7)	0.12‡
ACE III (Global Score)	91.9 (6.3)	89.7 (6.8)	88.3 (7.6)	0.69‡
ACE III cognitive subdomains				
Attention	17.2 (1.4)	17.3 (1.3)	17.1 (1.5)	0.69‡
Memory	22.6 (2.8)	22.9 (2.1)	22.5 (2.9)	0.79‡
Fluency	11.1 (1.9)	9.7 (1.6)	9.7 (2.1)	0.82‡
Language	24.8 (1.3)	25.2 (1.3)	24.9 (1.9)	0.68‡
Visuospatial	14.6 (1.8)	14.4 (2.0)	13.9 (2.6)	0.62‡
Weigl Color Form Sorting Test	3.6 (0.67)	3.6 (0.72)	3.5 (0.67)	0.81‡
TMT‡ (seconds)	42.9 (9.2)	44.2 (12.3)	44.3 (12.7)	0.38‡
TMT¶ (seconds)	101.1 (21.8)§	109.5 (20.1)**	112.9 (31.4)**	0.06‡

Categorical values are expressed as percentages or ratios. The mean ± SD and median values are reported for continuous variables. Lower mean scores represent a worse outcome for all tests except for the PHQ-9 and the TMT.
Because of the small numbers of patients in the Mild group (n= 10: eGFR 45 to < 60) they were combined with the Moderate group (N=38: 30 to <45) for ease of viewing.
*KIDIGO, Kidney Disease Improving Global Outcomes, stage of CKD: eGFR (estimated glomerular filtration rate) *Mild to Moderate 30 to <60: G3; Severe < 30: G4+5.
†Means across eGFR stages are equal = null hypothesis.
‡*P*-value calculated from ANOVA analysis of variance F-test.
§Numeric markers indicate significant differences between controls and CKD patients (by KIDIGO stage) within the same row, where '§' marked on a row are different from any other group not marked '**'.
¶P value calculated from χ^2 test.
ACE, Addenbrooke's Cognitive Examination; ANOVA, analysis of variance; CKD, chronic kidney disease; PHQ-9, Patient Health Questionnaire-9; TMT, Trail Making Tests.

and 20/143 (13.9%) in the control cohort. From baseline to follow-up, 19 (16.3%) of the CKD and 15 (10.5%) control subjects developed MCI. The diagnostic outcome of the CKD (outlined in online supplemental figure 2) cohort revealed five single domain MCI cases and the remaining patients had a multiple domain MCI. In the control cohort, four developed single and 11 developed multiple domain MCI. There were no differences observed between the two cohorts MCI diagnostic subtype (p=0.05). At follow-up, six cases of dementia were found in the CKD cohort and five cases in the control cohort. Application of DSM-5 classification revealed one case of AD in the CKD and four cases in the control cohort. Two of the CKD cohort and one control fulfilled criteria for vascular dementia, with the remaining CDK cases coded as dementia due to other aetiologies.

The risk compared with the controls for the development of an NCD of any type (MCI or Dementia) in the CKD cohort was 1.9 (95% CI 1.1 to 3.3), with an increased absolute risk of 21%. The RR in the CKD cohort for MCI was 1.9 (95% CI 1.0 to 3.5) and for dementia, it was 2.1 (95% CI .67 to 6.5). The incidence of new cases for NCD was calculated by summing the total person-years of the patients and controls in the study. The incidence rate for NCD of any type in the CKD cohort was 10.53 (95% CI 6.82 to 15.55) and in the control cohort, it was 5.1 (95% CI 3.1 to 7.7) per 100 person-years. The incidence for the development of an MCI was 8.0 (95% CI 4.82 to 12.5) in the CKD cohort and 3.75 (95% CI 2.1 to 6.2) in the controls. The CKD demented that cohort's incidence was 2.53 (95% CI 0.93 to 5.5) and, in the controls, it was 1.2 (95% CI 0.41 to 2.9).

An evaluation of the ACE III in both cohorts who fulfilled criteria for an NCD found an overall mean fall of 14.2 (±3.1) points in the CKD and 8.9 (±1.8) in the control groups (p<0.01). The cognitively normal CKD and controls were found to have a mean decrease in ACE III scores of 1.4 (±0.023) and 1.01 (±31) points, respectively (p=0.89). Examination of the cognitive domain predictors for the development of NCD in the CKD cohort from baseline to follow-up was performed in GLM models adjusting for age, education, gender, UACR, eGFR, IHD, HT and duration of CKD and diabetes. This revealed that memory (p<*0.*016), fluency (p<0.006) and executive function (p<0.001) impairments were strong predictors for NCD. A similar GLM was

performed with the control cohort, controlling for age, gender, education and HT. The strongest predictors for the development of NCD were memory (p<0.0001) and visuo-spatial impairments (p<0.02).

Cognitive impairment was observed more frequently at the advanced stage of CKD (eGFR<30), however, unadjusted χ^2 analysis did not reveal any a significant association with CKD stage and cognitive status (p=0.69). Additional unadjusted χ^2 analysis between MCI, dementia cases and eGFR stage did not reveal any significant associations (p=0.42). A longer duration of CKD was found to be significantly associated with dementia cases compared with the MCI (Z=2.76, p<0.004) and NCI cases (Z=2.53, p<0.012), however, not with the stage of CKD (p=0.05). The association with cognitive impairment and UACR was investigated with a Kruskal Wallis test, where significant differences between the impaired and non-impaired groups were observed (H(2) = 7.251, p<0.03). Further analysis employing group median analysis of the patients with CKD NCD found that patients with dementia compared with the non-impaired patients had significantly higher UACR's (Z=2.19, p<0.03). Lower HB concentrations controlling for age and gender were significantly associated with cognitively impaired patients (r=0.31, p<0.02). Further modelling was employed by dichotomising the data into groups with and without anaemia and entering this into GLM models controlling for demographic characteristics, HT, IHD, UACR and eGFR. This modelling revealed no significant associations with any of the cognitive domains or measures (p=0.05). A GLM investigating the GFR stage (CKD cohort) and NCD, controlled for age, education, gender, HT, IHD, HT and UACR, did not reveal revealed no significant associations (p=0.05). Additional analysis of the remaining clinical and blood markers (tables 1 and 2) did not reveal any significant predictive associations with the stage of CKD and (p=0.05).

DISCUSSION

Although cognitive impairment is commonly reported in CKD patient populations, the risk and incidence of

Table 2 Comparison between the blood and urine biomarkers of the CKD cohort (mean ± SD, ratios): n = 92

	Combined cohort (n=92)	G3* (n=48)	G4+5* (n=44)	P-value†
Duration of CKD	7.2±2.9	6.6±2.4‡	8.4±3.1††	0.04§
Duration of diabetes	19.6 (9.1)	19.3 (8.1)	20.3 (9.8)	0.23§
History of ischaemic heart disease	62:30	34:14	28:16	0.04¶
History of hypertension	75:17	40:8	35:9	0.35¶
Systolic BP mm Hg	147.7 (19.2)	138.2 (15.8)	148.6 (20.2)	0.06§
Diastolic BP mm Hg	74.7 (8.2)	71.4 (8.3)	73.5 (9.1)	0.67§
HbA1c mmol/mol	58.2 (16.2)	61.3 (12.3)	56.2 (15.8)	0.40§
Haemoglobin g/L	118.2 (13.2)	119.3 (10.9)††	113.2 (13.2)††	0.0001§
eGFR mL/min	28.4 (12.6)	42.5 (4.65)††	18.3 (6.5)††	0.0001§
Creatinine umol/L	215.7 (29.2)	140.1 (51.2)††	280.6 (93.3)‡	0.0001§
Urine ACR mmol/L, median	6.1	4.7	8.4	0.0001**
Albumin (serum) g/L	33.2 (4.7)	34.0 (4.1)	31.4 (4.5)	0.34§
Cholesterol mmol/L	3.9 (0.89)	4.0 (0.83)	4.0 (0.98)	0.51§
HDL	1.3 (0.44)	1.3 (0.43)	1.3 (0.43)	0.52§
NHDL	2.6 (0.79)	2.5 (0.69)	2.7 (0.88)	0.66§
LDL	1.9 (0.75)	1.8 (0.64)	2.0 (0.83)	0.29§
Triglyceride mmol/L	1.6 (0.75)	1.6 (0.87)	1.6 (0.69)	0.27§

Categorical values are expressed as percentages or ratios. The mean ± SD and median values are reported for continuous variables. Lower mean scores represent a worse outcome for all tests except for the PHQ-9 and the TMT.
Because of the small numbers of patients in the Mild group (n= 10: eGFR 45 to < 60) they were combined with the Moderate group (N=38: 30 to < 45) for ease of viewing.
*KIDIGO, Kidney Disease Improving Global Outcomes, stage of CKD: eGFR (estimated glomerular filtration rate). *Mild to Moderate 30 to <60: G3; Severe < 30: G4+5,
†Means across eGFR stages are equal = null hypothesis.
‡Markers indicate significant differences between controls and CKD patients (by KIDIGO stage) within the same row, where '‡' indicates a difference from another group on a particular row and '3' marked on a row are different from any other group not marked '††'.
§*P*-value calculated from ANOVA analysis of variance F-test.
¶P value calculated from χ^2 test.
**Kruskal Wallis test.
ACE, Addenbrooke's Cognitive Examination; ACR, albumin-creatinine ratio; ANOVA, analysis of variance; BP, blood pressure; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHDL, non-high-density lipoprotein; PHQ-9, Patient Health Questionnaire-9; TMT, Trail Making Tests.

developing an NCD have not received comparable attention.[8–10] We are not aware of any other study from the UK, where the risk and incidence of NCD in a cohort of moderate to advanced stage CKD (eGFR <60) patients with T2DM, compared with an age and gender-matched control group has been reported. This study found that 27% of the CKD and 14% of the control subjects fulfilled criteria for an NCD of any type at follow-up. The CKD cohort, compared with the controls, was found to have a twofold increased risk for developing significant cognitive impairment ranging from MCI to dementia. The incidence of new cases of NCD in the CKD cohort was 10.5 and 5.1 in the controls. The results of this study underline the importance of early assessment and recognition in clinical practice of the risk of developing an NCD in CKD. To address this, neuropsychological assessment should be incorporated into routine clinical practice.

We found that cognitive domains, memory, fluency and executive function impairment were found to be predictors for the development NCD in our CKD cohort. Whereas, in the control cohort, memory and visuospatial impairments were revealed as the strongest predictors, suggesting possible differing pathological and aetiological pathways in the MCI and the dementia type in CKD. The relationship between vascular changes in kidney, brain and cognitive function has been previously reported.[25 26] Cognitive impairment in the current investigation was not found to be associated with albuminuria and declining eGFR. Although others have explored this link, the results are often inconstant and indicate that further investigation is needed to address this possible association.[27 28] Other inflammatory markers, such as C reactive protein interleukin−1β and fibrinogen, have shown an association with an increased risk for cognitive impairment in CKD and other populations.[29 30] The current study did not measure these inflammatory markers and trying to unravel the undoubtedly multisystem risk factors and their causative risk factors were beyond the scope of the current study. Nevertheless, the findings here do suggest that further studies are needed to explore the contribution of vascular and inflammatory changes in the brain structures in CKD.

Although the current and our previous cross-sectional study did not find an association with cognitive impairment and CKD progression, other studies have reported this association.[9–12 31] This may reflect the methodological differences employed between this and previous investigations. In the current study, at baseline, only patients without an existing diagnosis of an NCD and an established diagnosis of T2DM were recruited into the investigation. In addition, compared with other studies, we included patients with moderate to advanced CKD with an eGFR <60 µmol/L, whereas other investigations have included patients with an eGFR >60, or at the end stage of the disease. Furthermore, other studies have often employed cross-sectional methodology alone and differing inclusion and exclusion criteria than ours and these investigations most likely have included cases with an existing cognitive impairment in their samples, possibly biasing the true prevalence in moderate to advanced stages of CKD.

Previous investigations have reported an association with Hb concentration and global cognitive function.[32 33] The current study found a relationship with lower Hb concentrations and global cognitive function, however, further analysis, controlling for demographics and clinical markers, did not support this relationship. This concurs with the CRIC study, where no independent relationship with anaemia and cognitive function was found.[34] The differences reported between the current and other studies are that ESRD patients receiving dialysis were included, existing cognitive impairment was not controlled for in their inclusion exclusion criteria, or analysis or have employed cross-sectional methodology alone.[32 33] This may have introduced bias, distorting the true relationship with CKD and Hb concentration. It is also worth considering that while anaemia is associated with CKD, it is instead part of the multiple metabolic physical dysfunctional changes occurring in CKD, rather than being an independent risk for the development of an NCD itself.

Strengths and weaknesses

The current study's strength is that it is the first longitudinal investigation in the UK to investigate the risk and incidence of NCD in a CDK cohort with concurrent T2DM, compared with an age and gender-matched control cohort. In addition, formal cognitive assessment and diagnostic outcomes were evaluated through the application of a battery of validated neuropsychological instruments, clinical consensus review and the application of DSM−5 criteria.

Our study does have some limitations. First, the absence of imaging to confirm or support the proposition that the cognitive impairments were as a result of vascular brain changes. Second, although the aim of the study was to the incidence and relative risk for NCD in CKD, it was not possible because of the sample size to establish other risks or factors that led to the development of NCDs. Third, residual confounding may have occurred because it was not possible to control for unmeasured comorbid conditions.

CONCLUSIONS

The strength of this study is its longitudinal design and the inclusion of patients and controls at baseline with normal cognitive function. Furthermore, we employed DSM-5 criteria to improve diagnostic accuracy, along with a battery of neuropsychological assessments to describe cases of NCD, controlling for potential confounders in the analysis. Although our results are not supportive of an association with the stage of CKD and NCD, they do nevertheless suggest that cognitive impairment is common in CKD, which needs to be carefully assessed and incorporated in the overall management of the condition. The pattern of cognitive impairment identified in this study may also act as a practical means to identify patients who are at risk of developing an NCD without the need for specialist referral. This is because they are measurable relatively quickly in normal clinical practice

and require modest upskilling among the clinical teams in their application, scoring and interpretation.

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Contributors PH and MK conceived and designed the study, collected the data and managed the database. PH and MK contributed to data cleaning and performed the statistical analyses. PH, SS, HN, SW and MK contributed to interpretation of the data. PH, SS, HN, SW and MK wrote the manuscript. All authors critically reviewed the manuscript and approved the final version to be published. PH is the guarantor for this study.

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