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Associations of Chronic Kidney Disease With Dementia Before and After Transient Ischemic Attack and Stroke: Population-Based Cohort Study

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ABSTRACT

Objective: Individuals with chronic kidney disease (CKD) appear to be at increased risk of cognitive impairment, with both vascular and neurodegenerative mechanisms postulated. To explore the vascular hypothesis, we studied the association between CKD and dementia before and after transient ischaemic attack (TIA) and stroke.

Methods: In a prospective, population-based cohort study of TIA and stroke (Oxford Vascular Study; 2002-2012), pre-event and new post-event dementia were ascertained through direct patient assessment and follow-up for 5 years, supplemented by review of hospital/primary care records. Associations between pre-event dementia and CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) were examined using logistic regression, and between post-event dementia and CKD using Cox and competing risk regression models, adjusted for age, sex, education, stroke severity, prior stroke, white matter disease, diabetes mellitus, and dysphasia.

Results: Among 2305 TIA/stroke patients (median [IQR] age, 77 [67-84] years, 1133 [49%] male, 688 [30%] TIA), 1174 (50.9%) had CKD. CKD was associated with both pre-event (odds ratio [OR], 2.04 [95% CI, 1.52–2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI, 1.65–2.44]; P<0.001), but these associations attenuated after adjustment for covariates (OR=0.92 [0.65-1.31]; p=0.65 and HR=1.09 [0.85-1.39]; p=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43-2.12; p<0.001, attenuating to 1.01 [0.78-1.33]; p=0.92 with adjustment). CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70-3.17; p<0.001), particularly after TIA and minor stroke (SHR=3.08, 2.05-4.64; p<0.001), but not significantly so after adjustment (SHR=1.53, 0.90-2.60; p=0.12).

Conclusions: In patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that renal-specific mechanisms are unlikely to play an important role in aetiology.

INTRODUCTION

Chronic kidney disease (CKD) is associated with a significant burden of cognitive impairment that worsens with declining renal function.[1] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, each 10mL/min/1.73 m^2 decrease in eGFR <60 mL/min/ 1.73m^2 was associated with an 11% increase in prevalence of cognitive dysfunction.[2] Haemodialysis patients are three times more likely to have severe cognitive impairment than age-matched non-dialysis patients with reported prevalence rates of 30-40%.[3]

Both vascular and neurodegenerative hypotheses have been proposed to underlie CKD-related cognitive impairment.[4, 5] In support of the vascular hypothesis, there is a high prevalence of cardiovascular risk factors[6] and a strong, blood-pressure dependent association with stroke in CKD.[7] Furthermore, impairment of executive function and processing speed are prominent in CKD, consistent with cerebrovascular disease.[8] Although CKD may also augment neurodegeneration through the interplay of hypertension and Alzheimer's pathology,[9] or via high concentrations of uraemic toxins such as neuroexcitatory guanidine compounds,[10] any association between CKD and dementia might simply be due to increased cerebrovascular disease associated with CKD. For example, silent cerebral infarction is increased in patients with CKD[11] and is associated with cognitive impairment.[12] However, in one previous study CKD was predictive of all-cause dementia independent of both previous symptomatic cerebrovascular disease and small vessel disease on brain imaging.[13] We therefore aimed to determine the associations between CKD and all-cause dementia before and after transient ischemic attack (TIA) or stroke, with adjustment for measures of severity of the initial event, vascular risk factors and other determinants of susceptibility in a large, longitudinal population-based study with standardized assessment of dementia to 5-years follow-up.

METHODS

Consecutive patients with TIA or stroke were prospectively recruited from April 1, 2002 to March 31, 2012 from the Oxford Vascular Study (OXVASC), an ongoing population-based study of all acute vascular events (including TIA, stroke, acute coronary syndromes, and peripheral vascular events). The study population comprises all 92,728 individuals, irrespective of age, registered with about 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. The methodology of OXVASC was approved by the Oxfordshire Research Ethics Committee. Multiple methods of ascertainment are used to ascertain patients with TIA or stroke, as detailed elsewhere.[14] Briefly, multiple overlapping methods of hot and cold pursuit are used to achieve near-complete ascertainment of all individuals with TIA or stroke and to minimize selection biases in determining dementia risk.[15] These include a daily, rapid access TIA clinic to which participating GPs and the local emergency department (ED) refer all individuals with unhospitalized TIA or stroke; daily searches of ward admissions (medical, cardiology, stroke unit, neurology), ED attendance register and in-hospital bereavement office death records; and monthly searches of death certificates, coroner's reports (for out-of-hospital deaths), GP and hospital diagnostic/discharge codes, and brain/vascular imaging referrals. Written informed consent (or assent from relatives) was obtained for study interview and follow-up, including ongoing review of all primary care/hospital records and centralized health and death data. Please see the *online-only eAppendix 1* for further details on the study population and case ascertainment methodology.

Patients were assessed by a study physician as soon as possible after their TIA/stroke, usually within one or two days of the event. TIA and stroke were defined using the World Health Organization criteria[16] (i.e. patients with infarction on brain imaging but symptoms lasting <24 hours were classed as TIA) with review of all cases by the same senior vascular neurologist (PMR) throughout the study (see the *online-only eAppendix 1* for definitions of events). A detailed clinical history was recorded in all patients by interview using a standardized questionnaire including education, medical history and vascular risk factors

were recorded in all patients, supplemented by primary care records (see the *online-only eAppendix 1*). Premorbid functional status was assessed using modified Rankin and Barthel scores, and stroke severity assessed with the National Institutes of Health Stroke Scale (NIHSS) score. Baseline brain and vascular imaging and other investigations were performed as reported previously.[14, 17]

CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[18] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). eGFR was then categorized into 5 groups based on modified CKD classification by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative: eGFR ≥ 90, 60-89, 30-59, 15-30 and <15 ml/min/1.73m^2. For the purpose of statistical analysis, eGFR ≥ 60 ml/min/1.73m^2 was used as the reference, as there were no post-stroke dementia events for eGFR ≥ 90 ml/min/1.73m^2 in some of the subgroup analyses. Similarly, the eGFR 15-30 and <15 ml/min/1.73m^2 groups were combined as the individual numbers within each group were small.

For details on the brain imaging see the *online-only eAppendix 1.* Assessments were made blind to clinical data. A qualitative scale was used (Oxford scale) based on the white matter disease severity score (absent, mild, moderate, or severe) of the Blennow scale for computed tomography scans and a modified version of the Fazekas scale for magnetic resonance imaging scans.[19]

Multiple methods of follow-up were used to reduce attritional biases in identification of dementia.[20] Follow-up interviews were done by trained nurses or study physicians at 1 month, 6 months, 1 year, and 5 years. If clinic follow-up was not possible, patients were assessed at home or via telephone. Cognitive function was tested with the mini-mental-state-examination (MMSE)[21] and Montreal Cognitive Assessment[22] at face-to-face interviews and with the telephone Montreal Cognitive Assessment and the Telephone Interview for Cognitive Status-modified.[23]

Dementia was defined as pre- or post-event according to whether the diagnosis was made before or after the index event, as described previously (see the *online-only eAppendix 1*).[15, 20, 24, 25] Briefly, pre-event dementia diagnosis was made using the following information: (1) baseline clinical assessment by study physician and discussion with relatives or other informant; (2) the presence of any dementia diagnosis, and related consultations and investigations, where available, in the primary care record, with hand-searching of the entire record including individual consultations, clinic letters, and hospitalization documentation. The diagnosis of pre-event dementia was made by an experienced consultant physician with subspecialty interest in dementia (STP) using the Diagnostic and Statistical Manual-IV (DSM-IV) criteria (e*Table 1*).

In patients without pre-event dementia, post-event dementia was diagnosed by STP using the same methodology (i.e. with clinical and cognitive assessment data and hand-searching of primary care records to death or 5-years' follow-up).[15, 20, 24, 25] MMSE was done at each follow-up interview, and dementia was diagnosed if MMSE was <24 and remained <24 for all subsequent follow-ups with fulfilment of other DSM-IV criteria including impairment of functional status.[15, 20, 24, 25] In patients who had problems that interfered with testing (e.g. dysphasia), incomplete testing (e.g. because of blindness), were followed up by telephone, could not be tested at the study interview (e.g. because of severe deafness) follow-up, or who did not have a follow-up assessment, dementia was diagnosed on the basis of study records where available and hand-searching of primary care, hospital and death records, based on Diagnostic and Statistical Manual-IV criteria (*eTable 1*).[15, 20, 24, 25]

Standard Protocol Approvals, Registrations, and Patient Consents

Received written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research).

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics stratified by CKD status and according to eGFR categories. Continuous data (standard deviation [SD]) or median (interquartile range [IQR]), and categorical data (n/%) were compared with Mann-Whitney U tests (or Kruskal-Wallis tests if multiple groups) and Chi-squared tests respectively. Age-adjusted P values for difference were calculated using logistic and linear regression where appropriate.

Associations between CKD and pre-event dementia were determined by binary logistic regression to generate ORs adjusted for (1) age, sex, and education (model 1) and (2) age, sex, education, and other factors previously reported as associated with pre-event dementia,[25] including white matter disease, prior stroke, diabetes mellitus, and also index stroke event severity (NIHSS) and dysphasia occurring after the index stroke (model 2).

All analyses involving post-event dementia were done after exclusion of cases of pre-event dementia. Cumulative incidence of dementia post-event was calculated by Kaplan-Meier methods censoring at death as described previously.[25] Cox regression was used to determine hazard ratios (HRs) for associations between overall 5-year risk of post-event dementia, and separately for early (≤1 year) and late (>1 year) post-event dementia (patients with late dementia were excluded from analyses of early dementia and vice versa). Regression analyses were adjusted (1) for age, sex, and education (model 1), (2) age, sex, education, and other factors reported as associated with dementia after TIA/stroke,[25] including stroke severity (NIHSS), white matter disease, dysphasia, prior stroke, and diabetes mellitus, and (3) with further adjustment for baseline cognitive test score (model 3). Similar analyses were done restricted to TIA and minor stroke (defined as NIHSS <3 as per OxVASC protocol) and major stroke (NIHSS ≥3).[25]

We did not examine primary intracerebral hemorrhage (PICH) separately owing to small numbers with this stroke subtype, but we undertook sensitivity analyses for pre- and post-event dementia in which PICH was excluded. We performed further sensitivity analyses excluding recurrent stroke on follow-up in analyses of post-event dementia.

Given that death is a competing risk for dementia (i.e. it precludes its occurrence), we performed exploratory analyses using competing risks regressions using cumulative incidence function (CIF) covariate analysis, similarly adjusted for the above covariates, to study the overall associations of CKD with post-event dementia and according to onset, early versus late post-event dementia.[33] From these regressions, we generated subdistribution hazard ratios (SHRs) for comparison as these are thought to be more informative of risk or prognosis whereas standard (cause-specific) HRs are thought to be better indicators of aetiology.[34]

Results were considered significant at $p < 0.05$. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL) and Stata version 13 (Stat Corp., College Station, TX).

Data Availability

Requests for access to data should be submitted for consideration to the OXVASC (Oxford Vascular Study) Study Director (peter.rothwell@ndcn.ox.ac.uk).

RESULTS

Of 2305 patients recruited from 2002-2012, 1133 (49%) were male, 688 (30%) had TIA, and 1617 (70%) had stroke of which 1482 were ischaemic stroke, and 135 were primary intracerebral haemorrhage (PICH). *Table 1* shows the baseline characteristics at the time of the event for all patients and according to CKD status. The median age was 76.9 years (IQR=66.9-83.9) and hypertension was the most prevalent risk factor being found in 1405 individuals (61%).

The median eGFR was 59.5 ml/min/1.73m^2. 1174 patients had CKD (50.9% of the study population, with eGFR of 30-59 ml/min/1.73m^2 in 1040 (45.2%) and <30 ml/min/1.73m^2 in 134 (5.8%). Only 12 patients (0.5%) were dialysis-dependent. Compared to those with

normal renal function, the CKD group were older and had a higher burden of vascular risk factors and co-morbidities including hypertension, diabetes mellitus, hyperlipidaemia, ischaemic heart disease, peripheral vascular disease, atrial fibrillation, and prior stroke. They were also more likely to have moderate-to-severe white matter disease, be less well-educated, and have a low baseline cognitive score. This burden of vascular and cognitive risk factors increased progressively with declining renal function, as evident when baseline demographics and co-morbidities were examined according to eGFR categories (*eTable 2)*.

Pre-event dementia was present in 225/2305 (9.8%) of patients. Compared with those with normal renal function, CKD was strongly associated with pre-event dementia on unadjusted analysis (OR=2.04, 95% CI=1.52-2.72; p<0.001) (*Table 2*), particularly at eGFR < 30 ml/min/1.73m^2 (Unadjusted OR=3.21, 1.96-5.26; p<0.001). However, all associations attenuated and became non-significant after adjustment for age, sex and education (model 1). After additional adjustment for other factors associated with pre-event dementia (model 2), there was further diminution of any association with CKD (OR= 0.92, 0-65-1.31; p=0.65; *Table 2*). Exclusion of PICH did not impact the results (*Table 2*). Stratifying by event severity, showed broadly similar associations (*Table 2*).

Excluding those with pre-event dementia, during 7,721 patient-years of follow-up (median/IQR=4.2/1.5-5.5), 432 patients developed post-event dementia (mean/sd age 82.1/8.7 years at diagnosis). There was a significantly greater risk of post-event dementia in patients with CKD compared to those with normal renal function (Log-rank p <0.001; *Figure 1*), and this was particularly marked in patients whose index event was a TIA or minor stroke (*eFigure 1*). However, although in unadjusted Cox regression analysis, CKD was strongly associated with post-event dementia to 5-years follow-up (HR=2.01, 95% CI 1.65-2.44; p<0.001 for all CKD), this association was also lost adjustment for age, sex and education, and other factors associated with post-event dementia (model 3 OR=1.09, 0.85-1.39; p=0.50) (e*Table 3*). Results were similar when PICH was excluded and when the 194 patients with recurrent stroke on follow-up, were excluded (*eTable 3*). CKD was more strongly associated with late (>1 year) vs early (<1 year) post-event dementia (HR=2.63, 1.96-3.53, p<0.001 vs 1.60, 1.23-2.09, p=0.001) (*eTable 4*), but the associations were also

lost after adjustment (model 3, HR=1.40, 0.98-2.00, p=0.06 for late dementia vs 0.90, 0.64-1.28, p=0.57 for early dementia).

The results were qualitatively and quantitatively similar when analyses were repeated using competing risk regressions (*Tables 3 and 4*). CKD was again associated with post-event stroke in the unadjusted model (SHR=1.74, 1.43-2.12; p<0.001) but not in the multivariate-adjusted models (SHR=0.97, 0.79-1.20; p=0.77, 0.94, 0.76-1.17; p=0.60; and 1.01, 0.78-1.33; p=0.92, for models 1, 2 and 3, respectively) (*Table 3*). The crude associations between eGFR categories and post-event dementia were weaker than those from the cause-specific hazards model, particularly for eGFR < 30 ml/min (SHR=1.51, 0.98-2.30 vs HR=2.48, 1.62-3.78). However, as per the cause-specific models, there were no independent associations between eGFR categories and post-event dementia after multivariate adjustment (*Table 3*). Restricting analysis to only ischaemic or major stroke events produced similar results. Competing risk analysis for early (<1 year) versus late (>1 year) post event dementia is shown in *Table 4* where CKD is again more strongly associated with later events (SHR=2.32, 1.70-3.17; p<0.001 vs 1.42, 1.10-1.83; p=0.01) but the association did not reach significance after complete adjustment (SHR=1.47, 0.99-2.18; p=0.06). CKD was particularly associated with late post-event dementia in the TIA and minor stroke subgroup (SHR=3.08, 2.05-4.64; p<0.001), attenuating with adjustment for age, sex, education, stroke severity, prior stroke, white matter disease, diabetes, and dysphasia (SHR=1.70, 1.05-2.76; p=0.03), and with additional adjustment for baseline cognitive score (SHR=1.53, 0.90-2.60; p=0.12).

DISCUSSION

In a large, prospective, population-based cohort study, CKD was not independently associated with either pre- or post-event dementia in patients with TIA and stroke. Associations were greatly attenuated after adjustment for age, sex, education, and other factors previously shown to be associated with dementia including stroke severity and white matter disease,[25] suggesting that renal-specific neurodegenerative mechanisms are unlikely to play an important role in the relationship between CKD and dementia, at least not in mild-to-moderate pre-dialysis stages. However, the consistently higher prevalence rates of pre- and post-event dementia in CKD patients does identify them as a vulnerable group.

Although CKD has been consistently associated with an increased risk of cognitive decline,[2, 26, 27] we did not find a strong independent association with dementia in our study, even at greater levels of renal dysfunction or when restricted to major stroke events. There a number of potential explanations for this discordance. Firstly, most of the cognitive studies to date have focused on the relationship between CKD and mild cognitive impairment (MCI) rather than dementia.[28, 29] Secondly, in contrast to our study, where most patients had pre-dialysis CKD and the majority had stage 3 (mild) CKD, previous dementia studies have been mainly dialysis-based.[30, 31] Dialysis patients have unique additional risk factors intrinsic to the dialysis procedure including cerebral hypoperfusion and this intradialytic hemodynamic instability causes transient 'cerebral stunning', leading to cumulative ischemic white matter changes and cognitive changes over time.[32] Thirdly, although we did not see an association between more advanced CKD and dementia, this is in keeping with the literature that suggests that duration of kidney disease or the rate of eGFR decline correlate better with cognitive dysfunction than severity of CKD.[33, 34]

Mechanisms underlying the pathogenesis of MCI and dementia in CKD are poorly understood. It has been proposed that uraemic neurotoxins interacting with neural progenitor cells, the brain vasculature, the glymphatic system and monoaminergic neurons may play a role.[35] High concentrations of uraemic toxins such as tumour necrosis factor (TNF) can impair synapse function and memory.[36] The glymphatic clearance of waste products occurs

primarily during sleep and CKD is associated with sleep disorders.[37] In addition, high levels of the circulating phosphaturic hormone fibroblast growth factor 23 (FGF-23), often found in CKD, have been associated with incident dementia.[38] However, the absence of an independent association between CKD and dementia in our TIA/stroke patients questions any renal-specific mechanisms over and above the effects of CKD on cerebovascular disease itself. For example, our associations were stronger for late (>1 year) post-event dementia, particularly in the TIA and minor stroke subgroup in whom new vascular dementia is often related to recurrent strokes or progressive cerebral small vessel disease (SVD).[39] Severe SVD has been implicated as the most important mechanism in late post-stroke dementia[40] and is strongly associated with CKD, especially at younger ages.[41]

In addition to the large study size, population-based design, and comprehensive adjustment for potential confounders, and detailed consideration of various biases in detection of dementia,[26-29] a further strength of our study is the inclusion of a competing risk analysis to account for the risk of death - the importance of which is being increasingly recognized in survival analyses of CKD given the high baseline mortality rate.[42, 43] The results from the competing risk analysis were qualitatively and quantitatively similar to those from the Cox (cause-specific) proportional hazards model with the exception of the associations between advanced CKD (eGFR < 30 ml/min/1.73m^2) and post-event dementia which decreased. This likely reflects the stronger association between advanced CKD and the competing event (i.e. death) resulting in lower SHRs than expected,[44] and is consistent with the findings in a previous study relating dialysis to risk for developing dementia.[43]

However, our study has a number of limitations. Firstly, TIA/stroke and dementia diagnoses were adjudicated by PMR and STP, respectively rather than by a consensus panel but this ensured consistent diagnosis over the 15-year time period of this study. Secondly, pre-event dementia was retrospectively diagnosed but the use of multiple sources should have minimised misclassification. Thirdly, we did not study the relationship between CKD and specific subtypes of dementia because clinical classification is challenging in older patients and mixed pathology is the most common finding in neuropathological studies.[45] Moreover, most dementia occurring after stroke is coded as being of “unspecified” cause in routine

practice.[35] Fourthly, we were unable to measure urine albumin excretion which some studies suggest is more strongly and independently associated with cognitive dysfunction than eGFR.[46, 47] Fifthly, as most of the CKD population had only mild-to-moderate disease, we may not have captured independent associations with dementia that may exist in later stages or in those who are dialysis-dependent. In addition, this was a highly select population enriched with vascular risk factors and therefore, the results may not be entirely generalizable to less multi-morbid CKD patients. Sixthly, as GFR was estimated from serum creatinine, this can lead to an overestimation of GFR in those with low muscle mass.[48] Since muscle mass loss is also associated with cognitive decline,[49] this may have underestimated the effect size of any association between CKD and cognitive decline. Our study should ideally be replicated using GFR estimated from cystatin-C molecule independent of muscle mass, which may increase precision of eGFR equations and has also been shown to colocalize with beta-amyloid in the brain.[50]

In conclusion, dementia is more common in patients with CKD than in the general population but pre-dialysis CKD itself appears not to be independently associated with either pre- or post-stroke dementia, except possibly with late-onset dementia in those with minor stroke events. Patients with CKD appear to have a clustering of risk factors associated with dementia including pre-stroke factors (advanced age, diabetes, and atrial fibrillation), stroke factors (greater event severity, dysphasia, and disability), and lower brain reserve (low education, pre-morbid dependency, and leukoareosis) that likely mediate much of the unadjusted relationship between CKD and dementia. Further studies are needed to determine if there are additional unique mechanisms or pathways leading to late-onset dementia in those with CKD and minor stroke events.

APPENDIX 1: AUTHORS

Name	Location	Contribution
Dearbhla M. Kelly, MBBChBAO, MSc, MRCPI	University of Oxford	Collected and analyzed the data, interpreted the results, drafted the manuscript for intellectual content.
Sarah T. Pendlebury, FRCP DPhil	University of Oxford	Major role in the acquisition and interpretation of data, revised the manuscript for intellectual content.
Peter M. Rothwell, MD PhD FRCP FMedSci	University of Oxford	Conceived and designed the study, provided supervision and funding, interpreted the data, and revised the manuscript for intellectual content.

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Table 1: Baseline characteristics of all patients with TIA and stroke, and stratified according to the presence of CKD

Characteristics*	All patients n= 2305	No CKD n= 1125	CKD present n= 1174	P value†
Age years, median (IQR)	76.9 (66.9-83.9)	69.9 (59.6-79.3)	81.4 (74.4-86.2)	<0.001
Age ≥ 75 years	1281 (55.6)	418 (37.2)	859 (73.2)	<0.001
Male sex	1133 (49.2)	659 (58.6)	474 (40.4)	<0.001
eGFR (ml/min/1.73m^2), median (IQR)	59.5 (46.3-73.5)	74.0 (66.7-84.1)	46.6 (38.2-53.6)	<0.001
Past history				
Hypertension	1405 (61)	589 (52.4)	814 (69.3)	<0.001
Diabetes mellitus	328 (14.2)	142 (12.6)	186 (15.8)	0.03
Hyperlipidaemia	683 (29.6)	299 (26.6)	384 (32.7)	0.002
Angina	371 (16.1)	128 (11.4)	243 (20.7)	<0.001
Myocardial infarction	256 (11.1)	82 (7.3)	174 (14.8)	<0.001
Peripheral vascular disease	178 (7.7)	61 (5.4)	117 (10)	<0.001
Atrial fibrillation	469 (20.3)	150 (13.3)	319 (27.2)	<0.001
Current smoking	323 (14.1)	232 (20.7)	91 (7.8)	<0.001
Prior stroke	274 (11.9)	95 (8.4)	177 (15.1)	<0.001
Moderate/severe WMD on brain scan	699 (32.7)	287 (26.8)	411 (38.6)	<0.001
Current event				0.02
TIA	688 (29.8)	357 (31.7)	330 (28.1)	
Ischaemic stroke	1482 (64.3)	693 (61.6)	786 (67)	
Primary ICH	135 (5.9)	75 (6.7)	58 (4.9)	
NIHSS, median (IQR)	1 (0-5)	1 (0-4)	1 (0-5.1)	<0.001
Dysphasia	402 (17.5)	166 (14.8)	234 (20.1)	0.001
Education ≤ 12 years	1543 (67)	715 (63.6)	826 (70.4)	0.001
Rankin ≥ 3	473 (20.5)	151 (13.4)	321 (27.4)	<0.001
Barthel < 20	481 (20.9)	163 (15.5)	317 (30.8)	<0.001
Low baseline cognitive score	354 (20.7)	136 (15.5)	217 (26.1)	<0.001
Pre-event dementia	225 (9.8)	75 (6.7)	149 (12.7)	<0.001
Post-event dementia	432 (20.8)	158 (15)	273 (26.6)	<0.001
Post-event dementia, early	450 (19.5)	169 (15)	279 (23.8)	<0.001
Post-event dementia, late	657 (28.5)	233 (20.7)	422 (35.9)	<0.001
Time to death, y, median (IQR)	2.8 (0.9-5.5)	3.7 (1.5-5.5)	2.4 (0.4-5.5)	<0.001
Death < 31 d	255 (11.1)	71 (6.3)	180 (15.3)	<0.001

*Numbers are n (%) unless otherwise stated.
†P-values are from Chi-squared tests or Mann-Whitney U tests, as appropriate. Logistic/linear regression was used to adjust for age.
CCF indicates congestive cardiac failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICH, intracerebral haemorrhage; IQR, interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; TIA, transient ischaemic attack; WHD, white matter disease.

Table 2. Prevalence of pre-event dementia according to CKD status and eGFR category, unadjusted, and adjusted for age, sex, education (Model 1), and also for stroke severity, prior Stroke, white matter disease, diabetes mellitus, dysphasia (Model 2)

OR (95% CI)						
	Unadjusted	**P Value**	**Model 1**	**P Value**	**Model 2**	**P Value**
All patients, N=2305						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.04 (1.52-2.72)	<0.001	1.02 (0.74-1.40)	0.91	0.92 (0.65-1.31)	0.65
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.90 (1.40-2.56)	<0.001	0.96 (0.70-1.33)	0.81	0.88 (0.61-1.26)	0.48
eGFR < 30	3.21 (1.96-5.26)	<0.001	1.49 (0.88-2.52)	0.14	1.24 (0.88-2.52)	0.14
Excluding PICH, N=2170						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.00 (1.48-2.69)	<0.001	1.00 (0.72-1.38)	1.00	0.89 (0.62-1.28)	0.54
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.85 (1.36-2.51)	<0.001	0.94 (0.67-1.31)	0.71	0.85 (0.58-1.24)	0.40
eGFR < 30	3.20 (1.95-5.27)	<0.001	1.49 (0.88-2.53)	0.14	1.17 (0.65-2.12)	0.60
TIA and minor stroke only, N=1436						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.47 (1.53-3.98)	<0.001	1.06 (0.64-1.77)	0.82	0.97 (0.55-1.71)	0.91
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	2.46 (1.51-3.99)	<0.001	1.06 (0.63-1.78)	0.82	0.96 (0.54-1.71)	0.89
eGFR < 30	2.62 (0.97-7.11)	0.06	1.07 (0.38-3.03)	0.91	1.07 (0.33-3.43)	0.91
Major stroke (NIHSS ≥3) only, N=869						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	1.57 (1.08-2.29)	0.02	0.99 (0.66-1.50)	0.98	0.88 (0.56-1.38)	0.57
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.44 (0.97-2.13)	0.07	0.92 (0.60-1.40)	0.68	0.80 (0.50-1.29)	0.36
eGFR < 30	2.38 (1.31-4.31)	0.004	1.49 (0.79-2.79)	0.22	1.29 (0.65-2.56)	0.47

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; PICH, primary intracerebral haemorrhage.

Table 3. Subdistribution hazard ratios (HR) for 5-year incidence of post-event dementia accounting for the competing risk of death, according to CKD status and eGFR category, unadjusted and adjusted for age, sex, and education (Model 1), and also for stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia (Model 2), and Model 2 also adjusted for baseline cognitive score (Model 3)

Subdistribution HR (95% CI)								
	Unadjusted	**P Value**	**Model 1**	**P Value**	**Model 2**	**P Value**	**Model 3**	**P Value**
All patients, N=2080								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.74 (1.43-2.12)	<0.001	0.97 (0.79-1.20)	0.77	0.94 (0.76-1.17)	0.60	1.01 (0.78-1.33)	0.92
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.77 (1.45-2.16)	<0.001	0.99 (0.80-1.23)	0.96	0.97 (0.78-1.21)	0.80	1.03 (0.79-1.35)	0.82
eGFR < 30	1.51 (0.98-2.30)	0.06	0.76 (0.48-1.20)	0.24	0.70 (0.43-1.13)	0.14	0.85 (0.48-1.51)	0.57
Excluding PICH, N=1954								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.79 (1.46-2.19)	<0.001	0.97 (0.78-1.21)	0.81	0.96 (0.76-1.20)	0.71	1.03 (0.78-1.36)	0.83
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.82 (1.48-2.23)	<0.001	0.99 (0.80-1.25)	1.00	0.99 (0.79-1.25)	0.95	1.05 (0.79-1.39)	0.34
eGFR < 30	1.57 (1.02-2.41)	0.04	0.76 (0.48-1.21)	0.25	0.68 (0.41-1.11)	0.12	0.85 (0.47-1.52)	0.58
TIA and minor stroke only, N=1354								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.74 (2.04-3.69)	<0.001	1.28 (0.93-1.76)	0.13	1.32 (0.94-1.84)	0.11	1.20 (0.83-1.73)	0.34
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.75 (2.03-3.71)	<0.001	1.29 (0.93-1.78)	0.12	1.32 (0.94-1.86)	0.10	1.22 (0.84-1.76)	0.29
eGFR < 30	2.72 (1.45-5.08)	0.002	1.16 (0.60-2.25)	0.66	1.21 (0.60-2.44)	0.59	0.94 (0.41-2.12)	0.88
Major stroke (NIHSS ≥3) only, N=726								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.01 (0.77-1.31)	0.95	0.73 (0.55-0.96)	0.03	0.71 (0.53-0.94)	0.02	0.86 (0.59-1.24)	0.41
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.06 (0.81-1.39)	0.67	0.77 (0.58-1.02)	0.07	0.75 (0.56-1.00)	0.05	0.86 (0.59-1.26)	0.44
eGFR < 30	0.70 (0.39-1.26)	0.24	0.50 (0.27-0.92)	0.03	0.48 (0.26-0.89)	0.02	0.79 (0.37-1.71)	0.55

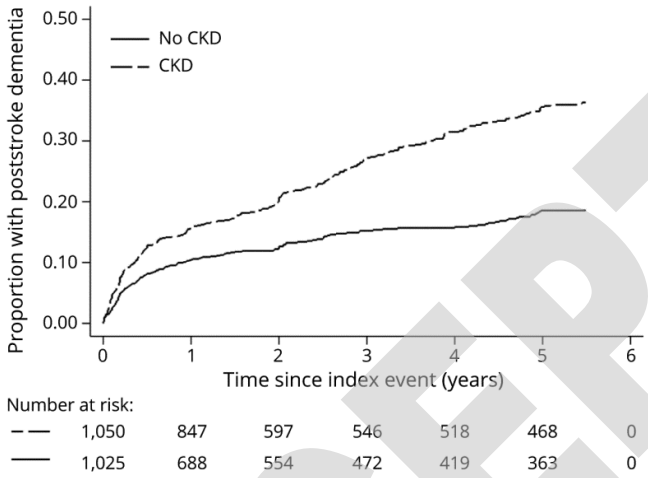
Table 4. Subdistribution HR for Early (≤1 Year) and Late (>1 Year) Postevent Dementia in patients with CKD accounting for the competing risk of death, unadjusted and adjusted for age, sex, and education (Model 1), and also for stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia (Model 2), and Model 2 also adjusted for baseline cognitive score (Model 3)

Subdistribution HR (95% CI)								
	Unadjusted	**P Value**	**Model 1**	**P Value**	**Model 2**	**P Value**	**Model 3**	**P Value**
All patients, N=2080								
Early Postevent Dementia (≤1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.42 (1.10-1.83)	0.01	0.74 (0.57-0.97)	0.03	0.70 (0.53-0.92)	0.01	0.75 (0.53-1.06)	0.10
eGFR≥60	1.41 (1.09-1.84)	0.01	0.75 (0.57-0.98)	0.03	0.72 (0.54-0.95)	0.02	0.75 (0.53-1.07)	0.11
eGFR 30-59	1.46 (0.85-2.52)	0.17	0.70 (0.39-1.23)	0.21	0.55 (0.30-1.04)	0.06	0.71 (0.33-1.53)	0.38
eGFR < 30	1.42 (1.10-1.83)	0.01	0.74 (0.57-0.97)	0.03	0.70 (0.53-0.92)	0.01	0.75 (0.53-1.06)	0.10
TIA and minor stroke only								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.38 (1.54-3.69)	<0.001	1.05 (0.67-1.66)	0.82	0.99 (0.63-1.55)	0.96	0.92 (0.56-1.51)	0.73
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.29 (1.47-3.59)	<0.001	1.02 (0.64-1.62)	0.93	0.97 (0.61-1.54)	0.90	0.90 (0.54-1.50)	0.69
eGFR < 30	3.38 (1.49-7.68)	0.004	1.42 (0.61-3.33)	0.42	1.20 (0.48-3.00)	0.70	1.11 (0.40-3.09)	0.84
Late Postevent Dementia (>1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.32 (1.70-3.17)	<0.001	1.47 (1.04-2.07)	0.03	1.46 (1.02-2.09)	0.04	1.47 (0.99-2.18)	0.06
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.41 (1.76-3.30)	<0.001	1.53 (1.08-2.15)	0.02	1.50 (1.05-2.15)	0.03	1.49 (1.00-2.23)	0.05
eGFR < 30	1.61 (0.82-3.14)	0.16	0.94 (0.46-1.91)	0.86	1.05 (0.51-2.15)	0.90	1.17 (0.54-2.56)	0.69
TIA and minor stroke only								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	3.08 (2.05-4.64)	<0.001	1.57 (1.00-2.46)	0.05	1.70 (1.05-2.76)	0.03	1.53 (0.90-2.60)	0.12
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	3.17 (2.10-4.78)	<0.001	1.61 (1.03-2.53)	0.04	1.74 (1.07-2.82)	0.02	1.59 (0.93-2.71)	0.09
eGFR < 30	2.15 (0.84-5.45)	0.11	1.04 (0.39-	0.93	1.26 (0.46-	0.65	0.86 (0.26-	0.80

			2.80)		3.39)		2.80)	

FIGURE

Figure 1: Kaplan-Meier (1-survival) curve showing the cumulative incidence of new post-event dementia (excluding pre-event dementia) for all patients (with and without CKD) to 5-years follow-up.



Associations of Chronic Kidney Disease With Dementia Before and After Transient Ischemic Attack and Stroke: Population-Based Cohort Study

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