

eAppendix 1

Associations of Chronic Kidney Disease with Dementia Before and After Transient Ischemic Attack and Stroke in a Population-Based Cohort Study

Dearbhla M. Kelly, MBBChBAO MSc MRCPI,¹ Sarah T. Pendlebury, FRCP DPhil,¹ Peter M. Rothwell, MD PhD FRCP FMedSci¹ on behalf of the Oxford Vascular Study.

¹Wolfson Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom.

Corresponding author:

Professor Peter Rothwell,

Wolfson Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom.

Tel no: +441865231601

Email: peter.rothwell@ndcn.ox.ac.uk

Cover title: CKD, Cerebrovascular Disease and Dementia

Key words: Chronic Kidney Disease; Stroke; Dementia; TIA; Cognition

TABLE OF CONTENTS

	Page Number
Supplemental Methods.....	3-8
Supplementary Figures	
eFigure 1: Kaplan-Meier (1-survival) curves 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, according to event severity: (A) TIAs (B) Minor strokes and (C) Major strokes.....	9
Supplementary Tables	
eTable 1: Diagnosis of dementia.....	10
eTable 2: Baseline characteristics of all patients with TIA and stroke, and stratified according to eGFR category.....	11
eTable 3: HRs for 5-Year Incidence of Postevent Dementia According to CKD Status and eGFR category.....	12
eTable 4: HR for Early (≤ 1 Year) and Late (> 1 Year) Postevent Dementia in patients with CKD.....	13

Supplemental Methods

OXVASC methodology

Study population

The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all incident acute vascular events in all territories (transient ischaemic attack, stroke, acute coronary and peripheral vascular events).¹⁻³

During the period of the current substudy, the OXVASC study population consisted of all 92,728 individuals, irrespective of age, registered with 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. In the UK, general practices provide primary health care for registered individuals and hold a lifelong record of all medical consultations (from the National Health Service [NHS] and private health care), and details of treatments, blood pressure, and investigations. In Oxfordshire, an estimated 97% of the true residential population is registered with a general practice, with most non-registered individuals being young students. All participating practices held accurate age-sex patient registers, and allowed regular searches of their computerised diagnostic coding systems. The practices had all collaborated on a previous population-based study, for which they were originally selected to be representative of the urban and rural mix and the deprivation range of Oxfordshire as a whole.⁴ Based on the index of multiple deprivation (IMD), the population was less deprived than the rest of England, but had a broad range of deprivation. The OXVASC population is 94% white people, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.⁴ The proportion of whites is similar to that of the UK as a whole (88% white) and to many other western countries (Australia - 90%; France - 91%; Germany - 93.9%).

Case ascertainment

After a 3-month pilot study, the study started on April 1, 2002, and is ongoing. Patients with TIA/minor stroke were referred directly by their primary care physician or the emergency department to dedicated daily OxVASC emergency clinics for acute management. Patients with major stroke were admitted to the regional acute hospital covering the study population and were recruited by daily hot pursuit. Ascertainment also combined prospective daily searches for acute events (hot pursuit) and retrospective searches of hospital-care and primary-care administrative and diagnostic coding data (cold pursuit).

Hot pursuit was based on:

1. A daily (weekdays only), urgent open-access "TIA clinic" to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.
2. Daily searches and case note review of admissions to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic, and Vascular Surgery wards, Acute Stroke Unit, Neurology ward and all other general wards when indicated.
3. Daily searches of the local A&E and eye hospital attendance registers.
4. Daily identification via the Bereavement Office of patients dead on arrival at hospital or who died soon after.
5. Daily searches of lists of all patients from the study population in whom a troponin-I level had been requested.

6. Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify both total burden of vascular invention and any potential missed prior acute events.

Cold pursuit procedures were:

1. Frequent visits to the study practices and monthly searches of practice diagnostic codes.
2. Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals.
3. Monthly listings of all referrals for brain or carotid imaging studies performed in local hospitals.
4. Monthly reviews of all death certificates and coroners reports to review out-of-hospital deaths.
5. Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. A study clinician assessed patients as soon as possible after the event in the hospital or at home. Informed consent was sought, if possible, or assent was obtained from a relative.

Baseline data collection form

Data are collected using event-specific forms, for TIA and stroke, acute coronary syndrome or acute peripheral vascular events. Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes details of the clinical event, medication, past medical history, education and occupational history, marital status, living arrangements, family history, functional status, abbreviated mental test score (AMTS), all investigations relevant to their admission (including blood results, electrocardiography, brain imaging and vascular imaging-duplex ultrasonography, CT-angiography, MR-angiography or DSA) and all interventions occurring subsequent to the event.

If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. If death occurred outside the hospital or before investigation, the autopsy result was reviewed. Clinical details are sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology. In a previous study, only 3/823 interviewed patients reported previous vascular events that had not been ascertained using these multiple methods, thus the ascertainment rate is >99% of events presenting to medical attention.³

All surviving TIA and stroke patients are followed-up face-to-face at 1, 6, 12, 60 and 120 months after the initial event by a research nurse or physician and all recurrent vascular events were recorded together with the relevant clinical details and investigations. If face-to-face follow up is not possible, telephone follow-up is performed or enabled via the general practitioner. Cognitive function is tested using MMSE and MoCA at face-to-face interview and T-MoCA and TICSm on telephone follow-up.^{5, 6} All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

Brain imaging and white matter disease severity grading

In the early years of the OxVASC study, CT was the default baseline brain imaging modality. In later periods, MRI was used. Therefore, methodology was developed to define the severity of leukoaraiosis in a reproducible manner whether the patient had received CT or MR brain imaging.⁷ Leukoaraiosis was prospectively and independently coded by a neuroradiologist and by an experienced neurologist. Assessments were made blind to clinical data.

Leukoaraiosis was graded according a qualitative scale (“Oxford scale”) based on the severity score (absent, mild, moderate, or severe) of the Blennow scale for CT scans, and a modified version of the Fazekas scale, considering periventricular and deep white matter lesions altogether, for MRI scans. Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by κ statistics in a subset of 996 consecutive cases and for MRI on 100 cases. We also performed an agreement study between CT and MRI in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted κ .

Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by κ statistics in a subset of 996 consecutive cases and for MRI on 100 cases. We also performed an agreement study between CT and MRI in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted κ .

The inter-rater agreement on presence of leukoaraiosis in 996 consecutive cases imaged by CT and rated by the Oxford scale was moderate to good ($\kappa = 0.64, 0.59\text{--}0.69$, for presence of any leukoaraiosis, and $0.58, 0.55\text{--}0.62$ for severity). The inter-rater agreement on presence of leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was also good ($\kappa = 0.78, 0.65\text{--}0.90$ for presence and $0.66, 0.56\text{--}0.76$ for severity of leukoaraiosis). In the 416 patients who had both CT and MRI, agreement between independent assessments made on the different modalities was not significantly less than the interobserver reproducibilities of either modality alone. Therefore, intra- and inter-rater reproducibility for both CT and MRI evaluations of leukoaraiosis was good as well as the concordance between the MRI and CT data.

Definitions of TIA/stroke events

Although new definitions for stroke and TIA have been suggested recently,^{8,9} in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout.⁹ A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.¹⁰ A TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.⁴ All cases were reviewed as soon as possible after presentation by the same senior neurologist (PMR) throughout the study. For the current analyses, we included patients who had definite or probable TIA as adjudicated by PMR and excluded patients with possible TIA. Brain imaging was not used to define TIA. With the high rate (97%) of imaging or autopsy in OXVASC, strokes of unknown type were coded as ischaemic.

Dementia diagnosis

We examined issues around measured dementia diagnosis with reference to the OxVASC methodology in three previous publications in Stroke, specifically the impact of selection¹¹ and attrition¹² biases and problems interfering with cognitive testing.¹³

In OxVASC, we used multiple methods of follow-up which have been shown to substantially reduce attritional biases in identification of dementia in OxVASC.¹² Dementia was defined as pre- or post-event according to whether the diagnosis was made before or after the index event.¹¹ Pre-event dementia diagnosis was made using the following information: i) baseline clinical assessment by study physician and discussion with relatives or other informant; ii) 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 hospitalisation documentation. In many cases, diagnosis was recorded in hospital notes or clinic letters but not in the primary care diagnosis list. In other cases, the diagnosis was made by STP on the basis of cognitive and functional impairment apparent from hand-searching of the medical record including individual primary care consultations or clinical hospital physician, nursing and allied health care professional records.

In patients without pre-event dementia, post-event dementia was diagnosed by STP using the same methodology (i.e. using the baseline and follow-up clinical and cognitive assessment data, supplemented by hand-searching of primary care records to death or 5-year follow-up). MMSE was done at each follow-up interview, and dementia was diagnosed if MMSE was <24 and remained <24 for all subsequent follow-ups in patients in whom cognitive testing was not affected by problems such as poor vision, hemiparesis or depression. A small number of subjects had a MoCA but no MMSE in whom none had dementia. In patients with telephone testing, incomplete testing or inability to perform a cognitive test at study interview (e.g. severe deafness) or with missing study follow-up assessment, dementia was diagnosed by STP on the basis of all available study assessment data and hand-searching of primary care, hospital and death records, based on DSM-IV criteria as described for pre-event dementia (*Supplemental Table I*).^{11, 12}

Regarding date of dementia diagnosis, although study interview did not routinely occur between 1 and 5 years after the index event, some patients had data from a study interview during this period because of a recurrent event. In other patients, details of a dementia diagnosis made between 1 and 5-year follow-up were obtained at the 5-year study follow-up and the date of diagnosis was obtained from medical records. For patients who did not have 5-year follow-up (eg because of death or drop-out between 1 and 5 years, untestability, telephone/email follow-up without a cognitive test), all available medical records were reviewed by STP. Where available, the exact date of diagnosis was recorded. If there was no clear date given in records, an approximate date of diagnosis was assigned based on review of study and medical records and information from informants where available.

We did not assess for functional impairment in patients diagnosed with dementia using the MMSE scores partly because it can be difficult attributing functional impairment to cognition versus physical disability in patients with cerebrovascular events. However, we performed sensitivity analyses to check whether this may have affected our results. Thirty-seven patients had low MMSE with a modified Rankin score of <2. In sensitivity analyses, removal of these patients had no significant effect on our findings and specifically, no impact on the relationship between event severity and dementia (HR=1.12 (1.10-1.13) per point increase in NIHSS vs 1.12 (1.10-1.13) adjusted for age, sex and education). Similarly, use of a lower cut-point (MMSE<20) in tested patients, did not change the relationship between event severity and post-event dementia (HR= 1.12 per point increase in NIHSS, p<0.0001).

For cases in which there was uncertainty (mainly in deciding whether cognitive impairment was sufficiently severe pre-event to be classed as pre-event dementia rather than

progressing post-event to dementia), all study and medical records information was reviewed and resolved by discussion between STP and PMR.

For this study, we did not identify Mild Cognitive Impairment (MCI) and such patients were not therefore included in the dementia diagnosis group.

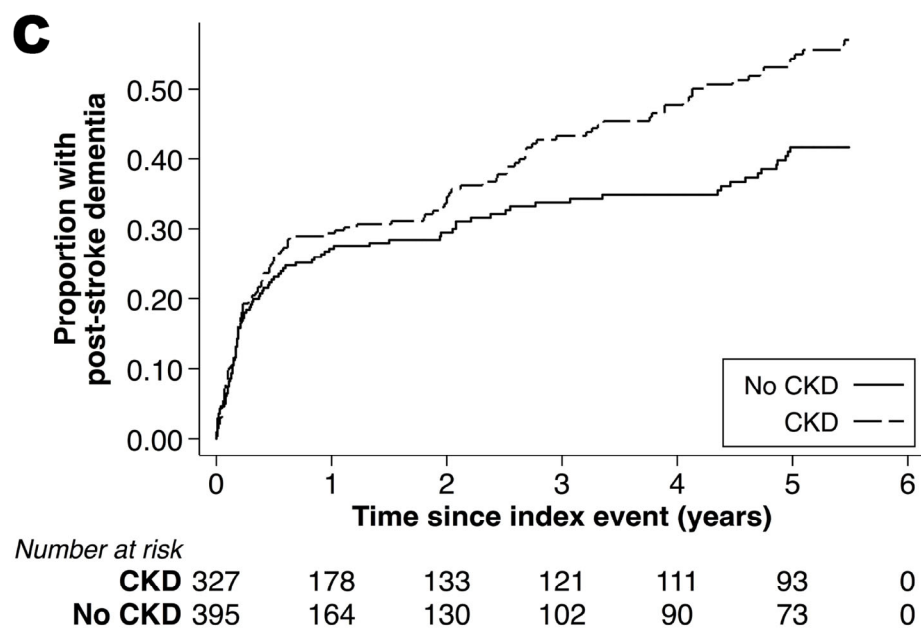
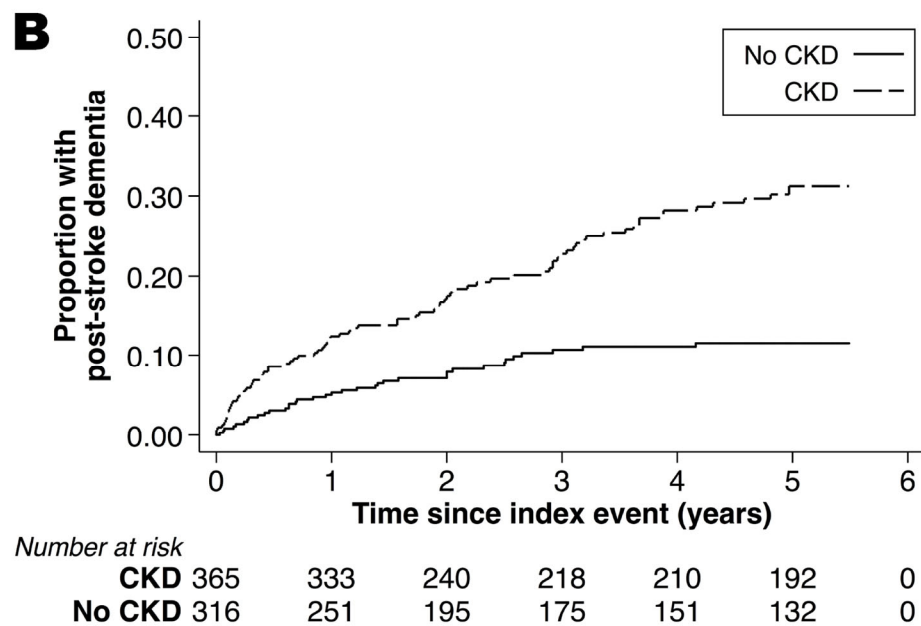
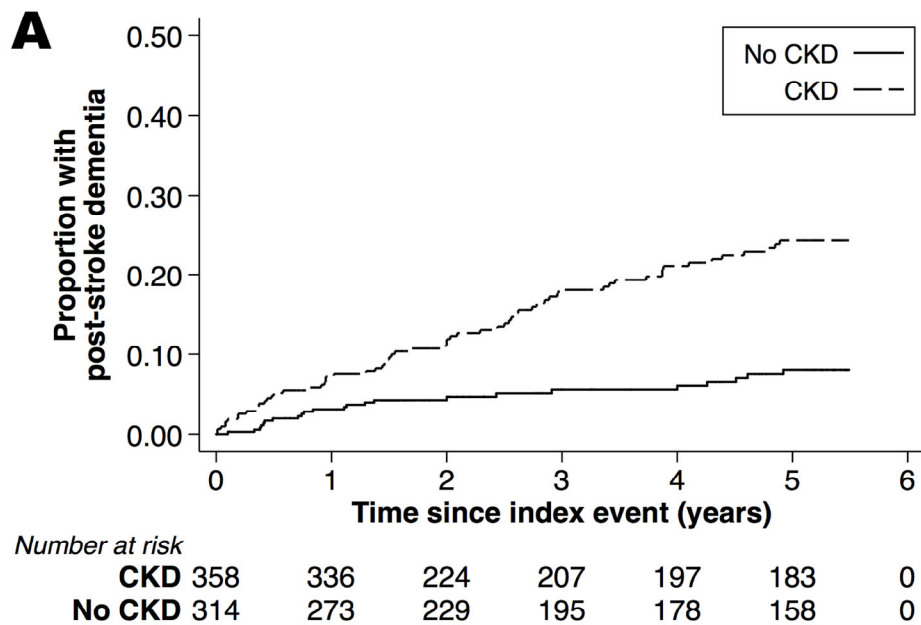
References:

1. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in oxfordshire, uk from 1981 to 2004 (oxford vascular study). *Lancet (London, England)*. 2004;363:1925-1933
2. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (oxford vascular study). *Lancet (London, England)*. 2005;366:1773-1783
3. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. *Stroke*. 2004;35:2041-2045
4. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: The oxfordshire community stroke project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *Journal of neurology, neurosurgery, and psychiatry*. 1990;53:16-22
5. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. Moca, ace-r, and mmse versus the national institute of neurological disorders and stroke-canadian stroke network vascular cognitive impairment harmonization standards neuropsychological battery after tia and stroke. *Stroke*. 2012;43:464-469
6. Pendlebury ST, Welch SJ, Cuthbertson FC, Mariz J, Mehta Z, Rothwell PM. Telephone assessment of cognition after transient ischemic attack and stroke: Modified telephone interview of cognitive status and telephone montreal cognitive assessment versus face-to-face montreal cognitive assessment and neuropsychological battery. *Stroke*. 2013;44:227-229
7. Simoni M, Li L, Paul NL, Gruter BE, Schulz UG, Kuker W, et al. Age- and sex-specific rates of leukoaraiosis in tia and stroke patients: Population-based study. *Neurology*. 2012;79:1215-1222
8. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the american heart association/american stroke association stroke council; council on cardiovascular surgery and anesthesia; council on cardiovascular radiology and intervention; council on cardiovascular nursing; and the interdisciplinary council on peripheral vascular disease. The american academy of neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40:2276-2293
9. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2013;44:2064-2089
10. Hatano S. Experience from a multicentre stroke register: A preliminary report. *Bulletin of the World Health Organization*. 1976;54:541-553

11. Pendlebury ST, Chen PJ, Bull L, Silver L, Mehta Z, Rothwell PM. Methodological factors in determining rates of dementia in transient ischemic attack and stroke: (i) impact of baseline selection bias. *Stroke*. 2015;46:641-646
12. Pendlebury ST, Chen PJ, Welch SJ, Cuthbertson FC, Wharton RM, Mehta Z, et al. Methodological factors in determining risk of dementia after transient ischemic attack and stroke: (ii) effect of attrition on follow-up. *Stroke*. 2015;46:1494-1500
13. Pendlebury ST, Klaus SP, Thomson RJ, Mehta Z, Wharton RM, Rothwell PM. Methodological factors in determining risk of dementia after transient ischemic attack and stroke: (iii) applicability of cognitive tests. *Stroke*. 2015;46:3067-3073

Figure legends

eFigure 1: Kaplan-Meier (1-survival) curves 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, according to event severity: (A) TIAs (B) Minor strokes and (C) Major strokes



eTable 1. Diagnosis of pre-event and post-event dementia based on the Diagnostic and Statistical Manual-IV (DSM-IV) criteria

<p>Pre-event dementia</p> <p>The 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 following DSM-IV criteria were then applied to make the final diagnosis:</p> <p>A1. Memory impairment</p> <p>A2. At least one of the following:</p> <ul style="list-style-type: none"> - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning <p>B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.</p> <p>C. The cognitive deficits do not occur exclusively during the course of delirium.</p>
<p>Post-event dementia</p> <p>In patients without pre-event dementia, post-event dementia was diagnosed using the baseline and follow-up clinical and cognitive assessment data, supplemented by hand-searching of primary care records to death or 5-year follow-up.</p> <p>MMSE was done at each follow-up interview, and dementia was diagnosed if MMSE was <24 and remained <24 for all subsequent follow-ups in patients who otherwise fulfilled other DSM-IV criteria as follows:</p> <p>A1. Memory impairment</p> <p>A2. At least one of the following:</p> <ul style="list-style-type: none"> - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning <p>B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.</p> <p>C. The cognitive deficits do not occur exclusively during the course of delirium.</p> <p>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 DSM-IV criteria outlined above.</p>

eTable 2. Baseline characteristics of all patients with TIA and stroke, and stratified according to eGFR category

Characteristics*	All patients n= 2305	eGFR ≥ 90 n= 169	eGFR 60-89 n= 956	eGFR 30-59 n=1040	eGFR < 30 n=134	P value†
Age years, median (IQR)	76.9 (66.9-83.9)	54.5 (47.2-63.9)	72.6 (63.1-80.2)	81.3 (74.4-86.0)	82.5 (74.2-88.5)	<0.001
Age ≥ 75 years	1281 (55.6)	5 (3)	413 (43.2)	764 (73.5)	95 (70.9)	<0.001
Male sex	1133 (49.2)	113 (66.9)	546 (57.1)	418 (40.2)	56 (41.8)	<0.001
eGFR (ml/min/1.73m ²), median (IQR)	59.5 (46.3-73.5)	97.4 (92.9-105.5)	71.6 (65.7-79.2)	48.1 (41.4-54.4)	23.2 (17.2-26.9)	<0.001
Past history						
Hypertension	1405 (61)	67 (39.6)	522 (54.6)	708 (68.1)	106 (79.1)	<0.001
Diabetes mellitus	328 (14.2)	20 (11.8)	122 (12.8)	153 (14.7)	33 (24.6)	0.002
Hyperlipidaemia	683 (29.6)	33 (19.5)	266 (27.8)	346 (33.3)	38 (28.4)	0.001
Angina	371 (16.1)	10 (5.9)	118 (12.3)	117 (20.9)	26 (19.4)	<0.001
Myocardial infarction	256 (11.1)	9 (5.3)	73 (7.6)	145 (13.9)	29 (21.6)	<0.001
Peripheral vascular disease	178 (7.7)	6 (3.6)	55 (5.8)	92 (8.8)	25 (18.7)	<0.001
Atrial fibrillation	469 (20.3)	12 (7.1)	138 (14.4)	274 (26.3)	45 (33.6)	<0.001
Current smoking	323 (14.1)	72 (42.9)	160 (16.8)	83 (8)	8 (6)	<0.001
Prior stroke	274 (11.9)	7 (4.1)	88 (9.2)	153 (14.7)	24 (17.9)	<0.001
Moderate/severe WMD on brain scan	699 (32.7)	18 (11.2)	269 (29.6)	358 (37.7)	53 (45.3)	<0.001
Current event						
TIA	688 (29.8)	48 (28.4)	309 (32.3)	302 (29)	28 (20.9)	0.008
Ischaemic stroke	1482 (64.3)	106 (62.7)	587 (61.4)	683 (65.7)	103 (76.9)	
Primary ICH	135 (5.9)	15 (8.9)	60 (6.3)	55 (5.3)	3 (2.2)	
NIHSS, median (IQR)	1 (0-5)	1 (0-3)	1 (0-4)	1 (0-5)	4 (0-10)	<0.001
Dysphasia	402 (17.5)	24 (14.3)	142 (14.9)	201 (19.5)	33 (24.6)	0.004
Education ≤ 12 years	1543 (67)	98 (58)	617 (64.6)	724 (69.7)	102 (76.1)	0.001
Rankin ≥ 3	473 (20.5)	15 (9)	136 (14.2)	269 (25.9)	52 (38.8)	<0.001
Barthel < 20	481 (20.9)	12 (7.6)	151 (16.9)	271 (29.2)	46 (45.1)	<0.001
Low baseline cognitive score	354 (20.7)	9 (6.6)	127 (17.2)	193 (25.4)	24 (34.8)	<0.001
Pre-event dementia	225 (9.8)	5 (3)	70 (7.3)	124 (11.9)	25 (18.7)	<0.001
Post-event dementia	432 (20.8)	6 (3.7)	152 (17.2)	248 (27.1)	25 (22.9)	<0.001
Post-event dementia, early	450 (19.5)	8 (4.7)	161 (16.8)	239 (23)	40 (29.9)	<0.001
Post-event dementia, late	657 (28.5)	11 (6.5)	222 (23.2)	372 (35.8)	50 (37.3)	<0.001
Death < 31 d	255 (11.1)	7 (4.1)	64 (6.7)	134 (12.9)	46 (34.3)	<0.001

*Numbers are n (%) unless otherwise stated.

†P-values are from Chi-squared tests or Kruskal-Wallis tests, as appropriate.

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.

eTable 3. HRs for 5-Year Incidence of Postevent Dementia According to CKD Status and eGFR category, Unadjusted and Adjusted for Age, Sex, Education (Model 1), and for Age, Sex, Education, Stroke Severity, Prior Stroke, White Matter Disease, Diabetes Mellitus, Dysphasia (Model 2), and Model 2 Adjusted for Baseline Cognitive Score (Model 3)

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)	2.01 (1.65-2.44)	<0.001	0.97 (0.79-1.19)	0.78	1.03 (0.83-1.28)	0.78	1.09 (0.85-1.39)	0.50
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.97 (1.61-2.41)	<0.001	0.96 (0.78-1.18)	0.70	1.02 (0.82-1.26)	0.88	1.08 (0.85-1.39)	0.53
eGFR < 30	2.48 (1.62-3.78)	<0.001	1.11 (0.72-1.70)	0.63	1.20 (0.77-1.86)	0.43	1.15 (0.69-1.92)	0.58
Excluding PICH, N=1954								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.08 (1.70-2.55)	<0.001	1.01 (0.81-1.24)	0.96	1.08 (0.87-1.35)	0.48	1.13 (0.88-1.45)	0.34
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.04 (1.66-2.51)	<0.001	0.99 (0.80-1.23)	0.94	1.07 (0.85-1.34)	0.57	1.12 (0.87-1.45)	0.37
eGFR < 30	2.59 (1.69-3.96)	<0.001	1.17 (0.76-1.79)	0.49	1.26 (0.81-1.96)	0.31	1.19 (0.71-1.98)	0.51
Excluding recurrent stroke on follow-up, N= 1607								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.26 (1.77-2.89)	<0.001	1.05 (0.81-1.35)	0.74	1.12 (0.86-1.47)	0.40	1.11 (0.81-1.51)	0.52
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.23 (1.74-2.86)	<0.001	1.04 (0.80-1.35)	0.77	1.12 (0.85-1.47)	0.42	1.13 (0.83-1.54)	0.45
eGFR < 30	2.68 (1.56-4.60)	<0.001	1.10 (0.64-1.91)	0.73	1.15 (0.65-2.04)	0.63	0.83 (0.40-1.75)	0.63
TIA and minor stroke only, N=1354								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.92 (2.16-3.95)	<0.001	1.26 (0.92-1.72)	0.15	1.32 (0.95-1.84)	0.10	1.20 (0.84-1.72)	0.31
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.89 (2.12-3.92)	<0.001	1.25 (0.91-1.72)	0.17	1.32 (0.95-1.84)	0.10	1.22 (0.86-1.75)	0.27
eGFR < 30	3.36 (1.81-6.25)	<0.001	1.32 (0.71-2.48)	0.38	1.32 (0.68-2.56)	0.41	0.98 (0.47-2.05)	0.96
Major stroke (NIHSS ≥3) only, N=726								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.38 (1.06-1.79)	0.02	0.79 (0.60-1.05)	0.10	0.86 (0.65-1.14)	0.30	0.97 (0.69-1.36)	0.85
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.34 (1.03-1.76)	0.03	0.78 (0.59-1.04)	0.09	0.82 (0.61-1.09)	0.17	0.94 (0.67-1.33)	0.73
eGFR < 30	1.74 (0.98-3.11)	0.06	0.95 (0.53-1.71)	0.86	1.07 (0.59-1.93)	0.84	1.29 (0.63-2.64)	0.49

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

eTable 4. HR for Early (≤ 1 Year) and Late (> 1 Year) Postevent Dementia in patients with CKD, Unadjusted and Adjusted for Demographic Factors (Model 1), and for Age, Sex, Education, Stroke Severity, Prior Stroke, White Matter Disease, Diabetes Mellitus, Dysphasia (Model 2), and Model 2 Adjusted for Baseline Cognitive Score (Model 3)

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)	1.60 (1.23-2.09)	0.001	0.79 (0.60-1.04)	0.09	0.88 (0.66-1.17)	0.37	0.90 (0.64-1.28)	0.57
eGFR ≥ 60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.55 (1.18-2.03)	0.002	0.76 (0.58-1.01)	0.06	0.86 (0.64-1.15)	0.31	0.89 (0.63-1.27)	0.52
eGFR < 30	2.24 (1.30-3.88)	0.004	1.06 (0.61-1.84)	0.84	1.06 (0.60-1.88)	0.85	1.05 (0.51-2.16)	0.89
Late Postevent Dementia (> 1 Year)								
No CKD (eGFR ≥ 60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.63 (1.96-3.53)	< 0.001	1.33 (0.98-1.82)	0.07	1.34 (0.96-1.86)	0.08	1.40 (0.98-2.00)	0.06
eGFR ≥ 60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.62 (1.94-3.53)	< 0.001	1.34 (0.98-1.84)	0.07	1.33 (0.95-1.86)	0.09	1.40 (0.98-2.01)	0.07
eGFR < 30	2.72 (1.40-5.29)	0.003	1.25 (0.64-2.47)	0.51	1.42 (0.72-2.82)	0.32	1.41 (0.68-2.92)	0.36

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.