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Age-Specific Associations of Renal Impairment With Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease in Transient Ischemic Attack and Stroke

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Background and Purpose—It has been hypothesized that cerebral small vessel disease (SVD) and chronic renal impairment may be part of a multisystem small-vessel disorder, but their association may simply be as a result of shared risk factors (eg, hypertension) rather than to a systemic susceptibility to premature SVD. However, most previous studies were hospital based, most had inadequate adjustment for hypertension, many were confined to patients with lacunar stroke, and none stratified by age.

Methods—In a population-based study of transient ischemic attack and ischemic stroke (OXVASC [Oxford Vascular Study]), we evaluated the magnetic resonance imaging markers of cerebral SVD, including lacunes, white matter hyperintensities, cerebral microbleeds, and enlarged perivascular space. We studied the age-specific associations of renal impairment (estimated glomerular filtration rate <60 mL/min per 1.73 m^2) and total SVD burden (total SVD score) adjusting for age, sex, vascular risk factors, and premorbid blood pressure (mean blood pressure during 15 years preevent).

Results—Of 1080 consecutive patients, 1028 (95.2%) had complete magnetic resonance imaging protocol and creatinine measured at baseline. Renal impairment was associated with total SVD score (odds ratio [OR], 2.16; 95% confidence interval [CI], 1.69–2.75; $P<0.001$), but only at age <60 years (<60 years: OR, 3.97; 95% CI, 1.69–9.32; $P=0.002$; 60–79 years: OR, 1.01; 95% CI, 0.72–1.41; $P=0.963$; ≥80 years: OR, 0.95; 95% CI, 0.59–1.54; $P=0.832$). The overall association of renal impairment and total SVD score was also attenuated after adjustment for age, sex, history of hypertension, diabetes mellitus, and premorbid average systolic blood pressure (adjusted OR, 0.76; 95% CI, 0.56–1.02; $P=0.067$), but the independent association of renal impairment and total SVD score at age <60 years was maintained (adjusted OR, 3.11; 95% CI, 1.21–7.98; $P=0.018$). Associations of renal impairment and SVD were consistent for each SVD marker at age <60 years but were strongest for cerebral microbleeds (OR, 5.84; 95% CI, 1.45–23.53; $P=0.013$) and moderate–severe periventricular white matter hyperintensities (OR, 6.28; 95% CI, 1.54–25.63; $P=0.010$).

Conclusions—The association of renal impairment and cerebral SVD was attenuated with adjustment for shared risk factors at older ages, but remained at younger ages, consistent with a shared susceptibility to premature disease. **(*Stroke*. 2018;49:899-904. DOI: 10.1161/STROKEAHA.117.019650.)**

Key Words: cerebral small vessel disease ■ chronic kidney disease ■ magnetic resonance imaging ■ stroke ■ transient ischemic attack

It has been hypothesized that cerebral small vessel disease (SVD) may be part of a multisystem disorder affecting other vascular beds, such as the kidney.[1,2] However, previous studies of the associations of chronic renal impairment and imaging makers of SVD were conflicting.[3–8] While some studies suggested that the association of renal impairment and SVD was explained by shared risk factors such as hypertension, others proposed that genetic factors might contribute to shared susceptibility. Any association caused by shared genetic susceptibility would usually be strongest at younger ages and should remain even after detailed adjustment for shared vascular risk factors.

Most previous studies of the association of renal impairment and SVD were hospital based, many had small numbers, the majority were confined to lacunar stroke patients, and all previous studies only adjusted for history of hypertension or

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a single recent blood pressure, which does not allow adequate adjustment for the potential confounding by long-term blood pressure burden. Moreover, few studies stratified the analyses by age, and no study has focused on the associations of renal impairment and cerebral SVD at younger ages.[7–10]

Therefore, in a population-based study, the OXVASC (Oxford Vascular Study), we studied patients with transient ischemic attack (TIA) and minor ischemic stroke to determine the age-specific associations of renal impairment and the overall burden of SVD (total SVD score),[9] as well as individual SVD markers, with adjustment for hypertension based on the average premorbid blood pressure level over many years, and by using both the premorbid and baseline creatinine measurement for the diagnosis of renal impairment.

Methods

Requests for access to data from OXVASC will be considered by the corresponding author.

We studied consecutive patients with TIA or ischemic stroke who underwent cerebral magnetic resonance imaging in OXVASC from 2004 to 2014. OXVASC is an ongoing population-based study of the incidence and outcome of all acute vascular events in a population of 92 728 individuals, registered with 100 general practitioners in 9 general practices in Oxfordshire, United Kingdom. The multiple overlapping methods used to achieve near complete ascertainment of all individuals with TIA and ischemic stroke and the imaging protocol of OXVASC are detailed in Methods in the online-only Data Supplement and have been reported previously.[11,12] All cases were reviewed by the senior study neurologist (Dr Rothwell), and TIA/stroke etiology was classified according to the modified Trial of ORG 10172 in Acute Stroke Treatment criteria.[11] For the current analyses, patients with cerebral or systemic vasculitis, Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy, or Fabry disease were excluded.

Demographic data, vascular risk factors (hypertension, diabetes mellitus, known atrial fibrillation, history of smoking, hyperlipidemia), history of previous TIA/stroke, and history of ischemic heart disease were collected from face-to-face interview and cross-referenced with primary care records. Patients routinely had creatinine measured after the acute event as part of the standard protocol. We also collected all premorbid blood pressure readings with dates up to at least 15 years before the event from patient records held in primary care. The most recent premorbid creatinine measurement within 1 year of the index event was also obtained from the regional biochemistry database.

The MDRD (Modification of Diet in Renal Disease) Study Group equation was used to calculate estimated glomerular filtration rate (eGFR) for each patient, and renal impairment was defined as estimated eGFR <60 mL/min per 1.73 m^2.[13] To minimize the potential impact of acute renal injury after TIA and ischemic stroke, we used creatinine taken at the time of the index event in the primary analysis, and the most recent premorbid creatinine taken within 1 year of the index event was also used for sensitivity analysis.

One neuroradiologist (Dr Kuker) provided ongoing supervision of interpretation of the magnetic resonance images throughout the study period, and the independently derived and proposed total SVD score was used to assess the overall burden of SVD.[9] One point is allocated to each of the following: (1) presence of lacunes; (2) presence of cerebral microbleeds (CMB); (3) moderate–severe (>10) basal ganglia (BG) perivascular spaces (PVS), and (4) severe periventricular or moderate–severe deep white matter hyperintensity (WMH). Lacunes were defined as rounded or ovoid lesions, >3 and <20 mm in diameter, in the BG, internal capsule, centrum semiovale, or brain stem, of cerebrospinal fluid signal density on T2 and fluid-attenuated inversion recovery and no increased signal on diffusion-weighted imaging.[14] CMBs were defined as rounded, hypodense foci up to 10 mm in size and were differentiated from microbleed mimics based on current guidelines.[15] PVSs were defined as small (<3 mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2 images in BG or centrum semiovale based on a previously validated scale,[16] and only BG-PVS were used in the total SVD score. The severity of white matter disease was determined for periventricular versus deep WMH, respectively, according to the Fazekas scale.[17]

Statistical Analysis

Categorical variables are reported as absolute numbers with percentages, and continuous variables are reported as means with SD. χ^2 and analysis of variance tests were performed to compare categorical and continuous variables between groups.

We first used ordinal regression to determine the age-specific (overall/stratified by age groups: <60, 60–79, and ≥80 years) associations of renal impairment and the total SVD score. We then used logistic regression to study the age-specific associations of renal impairment and individual SVD markers, including presence of lacunes, presence of CMBs, BG-PVS, moderate–severe periventricular WMH, and moderate–severe deep WMH. All analyses were adjusted for age (continuous/per year), sex, history of hypertension, diabetes mellitus, and 15-year premorbid systolic blood pressure.

All analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL).

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent or assent from relatives was obtained for all participants. OXVASC was approved by the local research ethics committee (OREC A: 05/Q1604/70).

Results

Among 1080 consecutive patients with TIA or ischemic stroke who underwent magnetic resonance brain imaging, 1028 (95.2%) had a full magnetic resonance imaging protocol completed and creatinine measured at baseline and were, thus, included in the analyses. Mean (SD) age was 68.4 (14.1) years, and 261 (26.7%) were <60 years. The baseline characteristics of patients stratified by the total SVD score are shown in Table 1.

As expected, patients with higher total SVD score were older, more likely to have history of hypertension, atrial fibrillation, TIA/stroke prior to the index event and history of ischemic heart disease (Table 1), and had higher blood pressure measured both acutely and during the 15 years before the index event (Table 1).

The eGFR decreased with increasing total SVD score using creatinine measured either at the index event or 1 year before the index event (both P_{trend}<0.001; Table 1). In an ordinal regression, renal impairment (eGFR<60 mL/min per 1.73 m^2) was associated with total SVD score (odds ratio [OR], 2.16, 95% confidence interval [CI], 1.69–2.75; P<0.001; Table 2), but this association was only apparent at age <60 years (<60 years: OR, 3.97; 95% CI, 1.69–9.32; P=0.002; 60–79 years: OR, 1.01; 95% CI, 0.72–1.41; P=0.963; ≥80 years: OR, 0.95; 95% CI, 0.59–1.54; P=0.832). The overall association of renal impairment and total SVD score was lost after adjustment for age and sex (OR, 0.94; 95% CI, 0.72–1.23; P=0.639; Table 2), and with additional adjustment for history of hypertension (OR, 0.85; 95% CI, 0.65–1.12; P=0.247; Table 2), and tended to be reversed when also adjusting for premorbid average systolic blood pressure (OR, 0.76; 95% CI, 0.56–1.02;

Table 1. Baseline Characteristics of Patients Included in Analyses Stratified by the Total SVD Score*

	All (N=1028)	SVD Score 0 (n=387)	SVD Score 1 (n=293)	SVD Score 2 (n=215)	SVD Score ≥3 (n=133)	*P* Value	P_{trend}
Age (mean±SD), y	68.4±14.1	59.3±14.2	71.3±11.0	75.5±9.8	77.4±10.3	<0.001	<0.001
Female	490 (47.7)	181 (46.8)	132 (45.1)	105 (48.8)	72 (54.1)	0.351	0.166
Hypertension	563 (54.8)	153 (39.5)	168 (57.3)	150 (69.8)	92 (69.2)	<0.001	<0.001
Hyperlipidemia	381 (37.1)	128 (33.1)	107 (36.5)	91 (42.3)	55 (41.4)	0.109	0.019
Diabetic mellitus	136 (13.2)	45 (11.6)	37 (12.6)	28 (13.0)	26 (19.5)	0.133	0.047
Ever smoker	521 (50.7)	204 (52.7)	133 (45.4)	120 (55.8)	64 (48.1)	0.085	0.803
Atrial fibrillation	160 (15.6)	28 (7.2)	52 (17.7)	50 (23.3)	30 (22.6)	<0.001	<0.001
TIA/stroke prior to the index event	187 (18.2)	47 (12.1)	49 (16.7)	53 (24.7)	38 (28.6)	<0.001	<0.001
History of ischemic heart disease	141 (13.7)	35 (9.0)	40 (13.7)	38 (17.7)	28 (21.1)	0.001	<0.001
Type of index event: ischemic stroke	486 (47.3)	165 (42.6)	133 (45.4)	108 (50.2)	80 (60.2)	0.004	<0.001
Etiology by TOAST classification						<0.001	NA
Large artery disease	137 (13.3)	32 (8.3)	48 (16.4)	38 (17.7)	19 (14.3)		
Cardioembolic	160 (15.6)	40 (10.3)	51 (17.4)	45 (20.9)	24 (18.0)		
Small vessel disease	124 (12.1)	35 (9.0)	27 (9.2)	29 (13.5)	33 (24.8)		
Cryptogenic	514 (50.0)	249 (64.3)	141 (48.1)	80 (37.2)	44 (33.1)		
Unknown etiology	26 (2.5)	10 (2.6)	6 (2.0)	6 (2.8)	4 (3.0)		
Multiple etiology	35 (3.4)	6 (1.6)	11 (3.8)	10 (4.7)	8 (6.0)		
Other etiology	32 (3.1)	15 (3.9)	9 (3.1)	7 (3.3)	1 (0.8)		
Baseline renal function							
eGFR (mean/SD; mL/min per 1.73 m^2)	71.4±22.3	77.4±21.9	71.3±21.4	65.6±20.6	63.7±23.1	<0.001	<0.001
eGRF<30	26 (2.5)	3 (0.8)	7 (2.4)	9 (4.2)	7 (5.3)	<0.001	<0.001
eGRF 30–59†	270 (26.4)	71 (18.4)	80 (27.4)	67 (31.3)	52 (39.4)		
eGRF 60–89	538 (52.5)	213 (55.2)	152 (52.1)	115 (53.7)	58 (43.9)		
eGRF≥90	190 (18.6)	99 (25.6)	53 (18.2)	23 (10.7)	15 (11.4)		
Renal impairment (eGFR<60)	300 (29.2)	75 (19.4)	88 (30.0)	77 (35.8)	60 (45.1)	<0.001	<0.001
Premorbid renal function							
eGFR (mean/SD; mL/min per 1.73 m^2)‡	68.1±20.3	72.6±20.5	69.1±20.7	63.7±19.1	62.8±18.3	<0.001	<0.001
eGRF<30	16 (1.7)	4 (1.2)	5 (1.9)	4 (2.0)	3 (2.4)	<0.001	<0.001
eGRF 30–59	313 (34.1)	82 (25.4)	95 (35.6)	80 (39.6)	56 (44.4)		
eGRF 60–89	469 (51.1)	182 (56.3)	126 (47.2)	100 (49.5)	61 (48.4)		
eGRF≥90	120 (13.1)	55 (17.0)	41 (15.4)	18 (8.9)	6 (4.8)		
Renal impairment (eGFR<60)	329 (35.8)	86 (26.6)	100 (37.5)	84 (41.6)	59 (46.8)	<0.001	<0.001
BP at index event (mean/SD)							
Systolic blood pressure, mm Hg	150.1±24.4	145.4±22.2	149.7±22.8	155.2±26.3	157.1±28.0	<0.001	<0.001
Diastolic blood pressure, mm Hg	83.8±13.2	84.8±13.3	82.7±12.1	84.2±13.5	82.5±14.7	0.184	0.178
All BP prior to the event (mean/SD)§							
Systolic blood pressure, mm Hg	138.7±14.3	132.7±13.7	143.2±12.0	148.0±13.6	148.0±13.6	<0.001	<0.001
Diastolic blood pressure, mm Hg	80.0±7.7	80.0±7.7	80.0±7.5	80.5±6.7	81.9±9.0	0.016	0.002

Data are presented as numbers (%) unless otherwise stated. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; NA, not applied; SVD, small vessel disease; TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Baseline characteristics of patients with renal impairment vs patients without renal impairment are also presented in Table I in the online-only Data Supplement.

†Four patients had eGFR classified as <60 only.

‡Based on one single creatinine in the last year and data missing for 110 patients.

§Data missing for 165 patients.

Table 2. Associations of Renal Impairment and Total SVD Score Stratified by Age and Adjusted for Age/Sex and for Known Vascular Risk Factors

	Crude		Model I*		Model II†		Model III‡	
	OR (95% CI)	*P* Value	OR1 (95% CI)	*P*1 Value	OR2 (95% CI)	*P*2 Value	OR3 (95% CI)	*P*3 Value
Overall	2.16 (1.69–2.75)	<0.001	0.94 (0.72–1.23)	0.639	0.85 (0.65–1.12)	0.247	0.76 (0.56–1.02)	0.067
Stratified by age								
<60 y	3.97 (1.69–9.32)	0.002	2.78 (1.15–6.73)	0.024	2.78 (1.15–6.73)	0.024	3.11 (1.21–7.98)	0.018
60–79 y	1.01 (0.72–1.41)	0.963	0.94 (0.72–1.23)	0.639	0.88 (0.62–1.25)	0.473	0.72 (0.49–1.06)	0.095
≥80 y	0.95 (0.59–1.54)	0.832	0.91 (0.56–1.47)	0.691	0.91 (0.56–1.47)	0.691	0.64 (0.37–1.12)	0.118

Renal impairment is defined as eGFR<60 mL/min per 1.73 m^2. CI indicates confidence interval; OR, odds ratio; and SVD, small vessel disease.
*Model I: adjusted for age and sex.
†Model II: adjusted for age, sex, and history of hypertension.
‡Model III: adjusted for age, sex, history of hypertension, diabetes mellitus, and premorbid mean systolic blood pressure.

P=0.067; Table 2). However, although the similar attenuation was observed for all age groups, the independent association of renal impairment and total SVD score was maintained in the multivariate analyses at age <60 years (adjusted OR, 3.11; 95% CI, 1.21–7.98; *P*=0.018; Table 2). Results were similar in patients with lacunar events and in those with nonlacunar events (Table II in the online-only Data Supplement).

When we looked at the associations of renal impairment and individual SVD markers, the results were also consistent, with attenuation of apparent associations after adjustment for known risk factors but with independent associations of renal impairment and SVD remaining at younger ages (Figure and Table III in the online-only Data Supplement), particularly for the presence of CMB (OR, 5.84; 95% CI, 1.45–23.53; *P*=0.013; Figure; Table III in the online-only Data Supplement) and for moderate–severe periventricular WMH (OR, 6.28; 95% CI, 1.54–25.63; *P*=0.010; Figure; Table III in the online-only Data Supplement).

Sensitivity analyses using creatinine measured 1 year prior to the index event also showed consistent results (Table IV and V in the online-only Data Supplement).

Discussion

In this population-based study of patients with TIA and ischemic stroke, we found that the associations of renal impairment (eGFR<60 mL/min per 1.73 m^2) and SVD were attenuated after adjustment for age, sex, known risk factors, and premorbid average blood pressure and disappeared at older ages. However, the association was maintained at age <60 years, both for the overall SVD burden and for individual SVD markers.

Our findings of age-specific associations of renal impairment and cerebral SVD in TIA and minor stroke are in line with previous studies done predominantly in lacunar stroke or in the nonstroke population using individual SVD markers. A rigorous and comprehensive systematic review and meta-analysis showed that the 4-fold increased risk of renal impairment in lacunar versus nonlacunar stroke was only observed at younger ages.[8] Similarly, in the nonstroke population, compared with studies of a mean age of 70 years, there was a stronger relationship between renal impairment and WMH in studies with an average age of 50 to 60 years.[8] The same pattern was also seen for renal impairment and CMB or enlarged PVS, where studies including younger patients tended to report a strong association[5,7] and studies of older cohorts tended to find no association.[4] However, one hospital-based study in TIA and ischemic stroke of a similar mean age to OXVASC (70 years versus 68.4 years) reported a strong association of proteinuria and CMB,[18] but only adjusted for history of diagnosed hypertension.

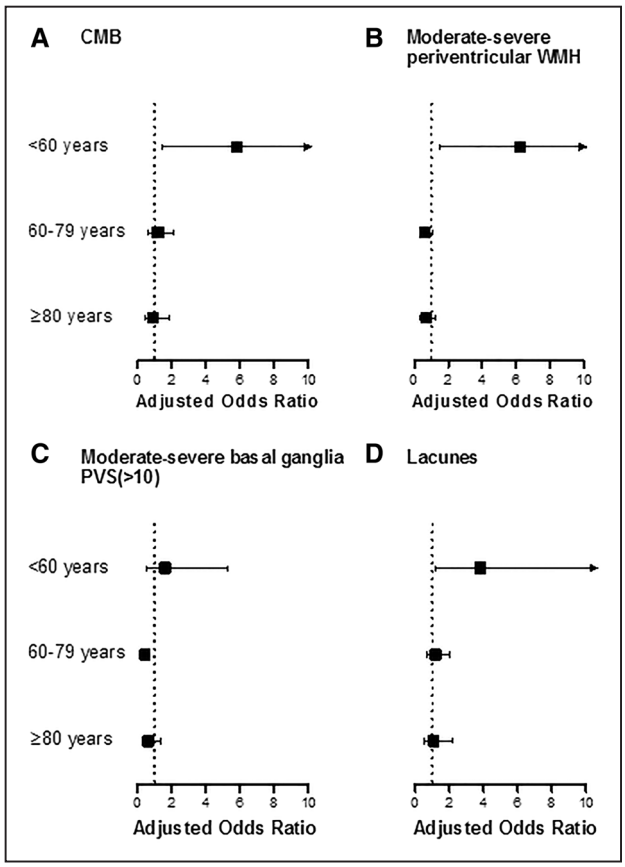

Figure. Associations of renal impairment (adjusted odds ratio and 95% CI) and the presence of individual small vessel disease markers stratified by age. Analyses were adjusted for age, sex, history of hypertension, diabetes mellitus, and premorbid mean systolic blood pressure. Renal impairment is defined as eGFR<60 mL/min per 1.73 m^2. CI indicates confidence interval; CMB, cerebral microbleeds; eGFR, estimated glomerular filtration rate; PVS, perivascular spaces; and WMH, white matter hyperintensity.

The reason why renal impairment correlates with SVD independent of hypertension and other vascular risk factors at younger ages is uncertain. One explanation is that rather than being the end organ damage from vascular risk factors such as hypertension in 2 different systems, renal impairment and cerebral SVD could be part of a multisystem disease directly affecting small vessels more generally. Our findings that the independent association of renal impairment and SVD seemed to be strongest in those presenting with acute small vessel disease (ie, acute lacunar event) also supported this hypothesis and are consistent with the previous systematic review of renal impairment and lacunar stroke.[8] Multisystem pathogenesis is also supported by associations of cerebral SVD with transforming growth factor-β signaling, which has also been associated with cancer, inflammation, and autoimmune diseases.[19,20] Alternatively, the independent associations of renal impairment and SVD at younger ages could similarly suggest shared susceptibility to vascular risk factors, most likely at the genetic level, leading to premature disease.

Notably, we did not observe any apparent associations of renal impairment and SVD at older ages. Moreover, after adjustment for age, sex, vascular risk factors, and premorbid blood pressure level, the association of renal impairment and SVD even showed a trend of reversed relationship at older ages. Given that both renal impairment and SVD are associated with premature death,[21] the nonassociation of renal impairment and SVD could be explained by a survival bias at older ages, where patients with stronger associations of renal impairment and SVD might have died at a younger age and were not therefore "available" to be recruited into the study. Similarly, patients with multiple comorbidities might also die prematurely, leaving those with fewer risk factors or less susceptibility to risk factors in the cohort, leading to a reverse association after adjustment for these risk factors.

A strength of our study is that we were able to adjust associations for long-term premorbid mean blood pressure, but there are also limitations. First, we used the creatinine-based MDRD calculation for eGFR. The MDRD equation was derived from a population with a mean age of 50.6±12.7 years.[22] Therefore, the eGFR calculation might not be sensitive enough to differentiate between normal aging-related renal impairment versus pathological renal impairment at older ages. However, the current clinical diagnosis of renal impairment is based on the same eGFR cutoff irrespective of age. Second, we did not measure cystatin C, which may be a more sensitive marker when the creatinine-based eGFR is between 45 and 59 mL/min per 1.73 m^2.[13] Therefore, we might have overestimated the true prevalence of renal impairment. Even so, we still found an independent association of renal impairment and SVD at younger ages. Third, we did not have data on proteinuria and used eGFR measurement after the acute event for the diagnosis of renal impairment. However, our sensitivity analyses using the eGFR prior to the index event showed consistent results. Fourth, we used the total SVD score to assess the burden of cerebral SVD. However, quantitative measurements of SVD markers might be more accurate in measuring the overall burden particularly for the more severe end. Fifth, although we adjusted for known confounding factors, the possibility of residual confounding could not be excluded. Moreover, we did not adjust for long-term blood pressure variability, although preliminary analyses do not suggest any significant confounding. Sixth, the multiple subgroup analyses were mainly for hypothesis generating and should therefore be interpreted with caution. Finally, our study is based in a predominantly White population and might not be generalizable to the Asian population, where there seems to be stronger association of renal impairment and SVD.

Our study has several implications. First, the independent associations of renal impairment and SVD at younger ages highlight the importance of effective renal function monitoring and management for young patients. Second, young patients with renal impairment and SVD could be potentially an interesting group for future genetic studies of small vessel disease, and future studies should stratify analyses by age. Finally, further research is needed to understand if there is age-specific treatment effect of renal impairment management on reducing the overall burden of cerebral SVD.

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Disclosures

None.

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Age-Specific Associations of Renal Impairment With Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease in Transient Ischemic Attack and Stroke

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SUPPLEMENTAL MATERIAL

Supplemental Method. 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).

The 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 adults. 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.[1] 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.[2] 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. Ascertainment 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.

Data is 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, 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.

All surviving 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. 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.

Definition of diagnosis

Although new definitions for stroke and TIA have been suggested recently,[2,3] in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout.[4] 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.[4] 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 diagnoses were reviewed by a senior neurologist (PMR). With the high rate (97%) of imaging or autopsy in OXVASC, strokes of unknown type were coded as ischaemic.

Brain imaging protocol

From April 1, 2002, to March 31, 2010 (phase 1), MRI and magnetic resonance angiography (MRA) was performed in selected patients when clinically indicated. From April 1, 2010 onwards (phase 2), brain MRI and MRA became the first-line imaging methods.[5] Patients were scanned predominantly with 2 scanners: Achieva (Philips Healthcare, Best, the Netherlands) and Magnetom Verio (Siemens health care, Munich, Germany).[6] The detailed sequence parameters are listed in the table below. One neuroradiologists (W.K.) provided ongoing supervision of interpretation of the MRI throughout the study period. The intra-rater κ for 50 randomly selected scans was as follows: lacunes 0.85; microbleed burden (0, 1, 2–4, ≥5) 0.88; periventricular WMH burden (Fazekas grade 0, 1, 2, 3) 0.66; subcortical WMH burden (Fazekas grade 0, 1, 2, 3) 0.75; PVS burden (<11, 11–20, >20) 0.86 (BG), 0.84 (CS).[7]

Table. Imaging sequence parameters used in OXVASC

MR parameters	OXVASC scanner 1 Magnetom Verio, Siemens Healthcare	OXVASC scanner 2 Discovery MR750, GE Healthcare	OXVASC scanner 3 Achieva, Philips Healthcare	OXVASC scanner 4 Signa HDxt, GE Healthcare
Patients scanned	388	62	493	137
Field strength (T)	3	3	1.5	1.5
T1W TR/TE/TI (ms)	2000/1.94/880	-	701/16	-
T2W TR/TE (ms)	6000/96	5800/94	5061/100	3760/100
FLAIR TR/TE/TI (ms) (3D)	9000/88/2500	9600/130/2350	11000/140/2800	8080/112/2200
Diffusion TR/TE (ms)	5300/91	6000/84	2891/73	6100/71
GRE / SWI TR/TE (ms) (3D)	GRE 504/15	GRE 500/20	GRE 694/23	GRE 560/25
Pixel bandwidth (Hz)	240 (T1W) 220 (T2W) 202 (FLAIR) 1374 (Diffusion) 200 (GRE)	- 50 (T2W) 41.7 (FLAIR) 250 (Diffusion) 31.3 (GRE)	87.4 (T1W) 88.5 (T2W) 375 (FLAIR) 25.3 (Diffusion) 109.3 (GRE)	- 47.6 (T2W) 31.3 (FLAIR) - 75 (GRE)
Matrix	256x256 (T1W) 320x320 (T2W) 192x192 (FLAIR) 130x130 (Diffusion) 320x256 (GRE)	- 512 (T2W) 384x224 (FLAIR) 128x128 (Diffusion) 288x224 (GRE)	118x214 (T1W) 356x193 (T2W) 236x159 (FLAIR) 97x84 (Diffusion) 256x163 (GRE)	416x256 (T2W) 256x224 (FLAIR) 128x128 (Diffusion) 288x192 (GRE)
No. of slices	208 (T1W) 25 (T2W) 50 (FLAIR) 25 (Diffusion) 25 (GRE)	25	25 (T1W) 25 (T2W) 28 (FLAIR) 25 (Diffusion) 22 (GRE)	25
Slice thickness (mm)	1 (T1W) 5 (T2W) 3 (FLAIR) 5 (Diffusion) 5 (GRE)	5	5	5
Inter-slice gap (mm)	0 (T1W) 1 (T2W) 0 (FLAIR coronal) 1 (Diffusion) 1 (GRE)	1	1	1
Voxel size (mm^3)	1.0x1.0x1.0 (T1W) 0.8x0.8x5.0 (T2W) 1.0x1.0x3.0 (FLAIR) 1.8x1.8x5.0 (Diffusion) 0.9x0.8x5.0 (GRE)	-	0.53x0.53x5.0 (T1W) 0.65x0.65x5.0 (T2W) 0.82x0.81x5.0 (FLAIR) 1.74x1.73x5.0 (Diffusion) 0.90x0.90x5.0 (GRE)	-

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Supplemental Table I. Baseline charateristics of patient with renal impairment vs. patients without renal impairment

	All	Patients with renal impairment	Patients without renal impairment	p
	(N=1028)	(n=300)	(n=728)	
Age (mean±SD; years)	68.4±14.1	76.7±9.9	65.0±14.1	<0.0001
Female	490 (47.7)	172 (57.3)	318 (43.7)	<0.0001
Hypertension	563 (54.8)	223 (74.3)	340 (46.7)	<0.0001
Hyperlipidemia	381 (37.1)	156 (52.0)	225 (30.9)	<0.0001
Diabetic mellitus	136 (13.2)	57 (19.0)	79 (10.9)	0.0005
Ever smoker	521 (50.7)	149 (49.7)	372 (51.2)	0.66
Atrial fibrillation	160 (15.6)	63 (21.0)	97 (13.3)	0.002
TIA/stroke prior to the index event	187 (18.2)	91 (30.3)	96 (13.2)	<0.0001
History of ischaemic heart disease	141 (13.7)	67 (22.3)	74 (10.2)	<0.0001
Type of index event – ischaemic stroke	486 (47.3)	151 (50.3)	335 (46.0)	0.21
Aetiology by TOAST classification				0.003
Large artery disease	137 (13.3)	58 (19.3)	102 (14.0)	
Cardioembolic	160 (15.6)	52 (17.3)	85 (11.7)	
Small vessel disease	124 (12.1)	31 (10.3)	93 (12.8)	
Cryptogenic	514 (50.0)	131 (43.7)	383 (52.6)	
Unknown aetiology	26 (2.5)	8 (2.7)	18 (2.5)	
Multiple aetiology	35 (3.4)	15 (5.0)	20 (2.7)	
Other aetiology	32 (3.1)	5 (1.7)	27 (3.7)	
SVD score				<0.0001
0	387 (37.6)	75 (25.0)	312 (42.9)	
1	293 (28.5)	88 (29.3)	205 (28.2)	
2	215 (20.9)	77 (25.7)	138 (19.0)	
≥3	133 (12.9)	60 (20.0)	73 (10.0)	
BP at index event (mean/SD)				
Systolic blood pressure (mmHg)	150.1±24.4	151.8±27.3	149.4±23.1	0.23
Diastolic blood pressure (mmHg)	83.8±13.2	80.7±13.3	85.1±13.0	<0.0001
All BP prior to the event (mean/SD)				
Systolic blood pressure (mmHg)	138.7±14.3	144.5±13.0	136.2±14.1	<0.0001
Diastolic blood pressure (mmHg)	80.0±7.7	80.0±7.0	80.1±7.9	0.84

*renal impairment is defined as eGFR<60 mL/min/1.73m^2

Supplemental Table II. Associations of renal impairment and total SVD score stratified by age in Lacunar vs. Non-lacunar events

	Lacunar						Non-lacunar					
	Crude		Model I*		Model II**		Crude		Model I*		Model II**	
	OR (95%CI)	p	OR1 (95%CI)	p1	OR2 (95%CI)	p2	OR (95%CI)	p	OR1 (95%CI)	p1	OR2 (95%CI)	p2
Overall	1.55 (0.75-3.20)	0.235	0.80 (0.37-1.73)	0.572	0.79 (0.35-1.80)	0.575	2.32 (1.78-3.01)	<0.001	0.95 (0.71-1.27)	0.727	0.74 (0.53-1.02)	0.066
Stratified by age												
<60y	16.04 (2.28-112.62)	0.005	21.28 (2.38-190.57)	0.006	14.01(1.31-149.45)	0.029	2.22 (0.78-6.32)	0.134	1.44 (0.49-4.25)	0.508	1.87 (0.59-5.91)	0.285
60-79y	0.48 (0.18-1.30)	0.150	0.44 (0.16-1.22)	0.114	0.46 (0.15-1.40)	0.171	1.15 (0.80-1.65)	0.441	0.98 (0.67-1.42)	0.903	0.73 (0.48-1.12)	0.148
≥80y	0.88 (0.17-4.70)	0.885	0.70 (0.13-3.87)	0.681	0.87 (0.11-6.56)	0.889	0.96 (0.58-1.59)	0.867	0.93 (0.56-1.54)	0.780	0.69 (0.38-1.25)	0.219

SVD=small vessel disease, OR=odds ratio, CI=confidence interval; *Model I: adjusted for age and gender; **Model II: adjusted for age, gender, history of hypertension, diabetes and premorbid mean systolic blood pressure.

Renal impairment is defined as eGFR<60 mL/min/1.73m^2

Supplemental Table III. Associations of renal impairment and the presence of individual small vessel disease markers stratified by age and adjusted for age/sex and for known vascular risk factors

	Renal impairment in those with SVD	Renal impairment in those without SVD		Model I*			Model II**		
	(n/total; %)	(n/total; %)	p	OR1	95%CI	p1	OR2	95% CI	p2
Cerebral microbleeds									
<60y	5/16 (31.3)	16/245 (6.5)	**0.001**	5.01	1.48-16.94	**0.010**	5.84	1.45-23.53	**0.013**
60-79y	30/83 (36.1)	125/466 (26.8)	**<0.001**	1.31	0.90-1.90	0.157	1.19	0.66-2.14	0.557
≥80y	32/57(56.1)	92/161 (57.1)	0.963	0.99	0.54-1.83	0.988	0.89	0.43-1.84	0.742
Moderate-severe periventricular WMH									
<60y	5/15 (33.3)	16/246 (6.5)	**<0.001**	5.62	1.90-16.73	**0.002**	6.28	1.54-25.63	**0.010**
60-79y	47/168 (28.0)	108/381 (28.3)	**<0.001**	0.92	0.62-1.38	0.696	0.65	0.40-1.05	0.079
≥80y	61/114 (53.5)	63/104 (60.6)	0.689	0.70	0.41-1.20	0.196	0.68	0.36-1.26	0.219
Moderate-severe subcortical WMH									
<60y	3/17 (17.6)	18/244 (7.4)	**0.031**	2.07	0.67-6.45	0.212	1.41	0.32-6.12	0.648
60-79y	48/164 (29.3)	107/385 (27.8)	0.300	1.02	0.68-1.52	0.925	0.79	0.49-1.29	0.346
≥80y	61/113 (54.0)	63/105 (60.0)	0.194	0.68	0.40-1.16	0.154	0.57	0.30-1.08	**0.084**
Moderate-severe basal ganglia PVS(>10)									
<60y	5/33 (15.2)	16/228 (7.0)	0.108	1.53	0.50-4.68	0.459	1.62	0.50-5.31	0.425
60-79y	74/300 (24.7)	81/249 (32.5)	**0.042**	0.56	0.37-0.83	**0.004**	0.45	0.29-0.71	**0.001**
≥80y	94/168 (56.0)	30/50 (60.0)	0.612	0.80	0.42-1.54	0.500	0.62	0.29-1.35	0.231
Lacunes									
<60y	7/29 (24.1)	14/232 (6.0)	**0.004**	3.42	1.20-9.75	0.022	3.81	1.21-12.04	**0.023**
60-79y	34/100 (34.0)	121/449 (26.9)	0.177	1.37	0.85-2.20	0.202	1.19	0.70-2.05	0.520
≥80y	35/53 (66.0)	89/165 (53.9)	0.151	1.66	0.87-3.18	0.125	1.08	0.52-2.22	0.836

SVD=small vessel disease, WMH=white matter hyperintensity, PVS= perivascular spaces, OR=odds ratio, CI=confidence interval; *Model I: adjusted for age, and gender; **Model II: adjusted for age, gender, history of hypertension, diabetes and premorbid mean systolic blood pressure. Renal impairment is defined as eGFR<60 mL/min/1.73m^2

Supplemental Table IV. Associations of renal impairment and total SVD score by age, using creatinine taken one year prior to the index event

	Crude			Model I*			Model II**		
	OR	**95%CI**	**p**	**OR1**	**95%CI**	**p1**	**OR2**	**95% CI**	**p2**
Overall	1.65	1.25-2.19	<0.001	0.87	0.64-1.19	0.377	0.73	0.52-1.04	0.079
Stratified by age									
<60 years	4.40	1.44-13.45	0.009	3.52	1.11-11.21	0.033	2.95	0.82-10.55	0.096
60-79 years	1.09	0.74-1.61	0.655	0.92	0.62-1.39	0.704	0.89	0.56-1.39	0.595
≥80 years	0.65	0.39-1.10	0.108	0.66	0.39-1.12	0.128	0.42	0.23-0.78	0.006

SVD=small vessel disease, OR=odds ratio, CI=confidence interval; *Model I: adjusted for age, gender; **Model II: adjusted for age, gender, history of hypertension, diabetes and premorbid mean systolic blood pressure. The first two groups of the total SVD (score 0 and 1) were combined for the ordinal regression. Renal impairment is defined as eGFR<60 mL/min/1.73m^2

Supplemental Table V. Associations of renal impairment and the presence of individual small vessel disease marker by age, using creatinine taken one year prior to the index event

	Renal impairment in those with SVD	Renal impairment in those without SVD		Model I*			Model II**		
	(n/total; %)	(n/total; %)	p	OR1	95%CI	p1	OR2	95% CI	p2
Cerebral microbleeds									
<60y	3/12 (25.0)	19/152 (12.5)	0.205	1.92	0.45-8.24	0.380	2.00	0.43-9.43	0.380
60-79y	27/70 (38.6)	130/403 (32.3)	0.336	1.19	0.69-2.04	0.540	0.91	0.50-1.68	0.772
≥80y	30/56 (53.6)	97/147 (66.0)	0.108	0.63	0.34-1.18	0.150	0.59	0.28-1.23	0.158
Moderate-severe periventricular WMH									
<60y	4/14 (28.6)	18/150 (12.0)	0.098	2.22	0.67-7.33	0.193	2.46	0.58-10.44	0.221
60-79y	53/150 (37.3)	104/323 (32.2)	0.530	1.00	0.66-1.52	0.992	0.85	0.53-1.35	0.486
≥80y	63/108 (58.3)	64/95 (67.4)	0.194	0.68	0.39-1.21	0.189	0.69	0.36-1.31	0.254
Moderate-severe subcortical WMH									
<60y	3/13 (23.1)	19/151 (12.6)	0.386	1.43	0.40-5.08	0.583	1.67	0.40-6.94	0.483
60-79y	45/141 (31.9)	112/332 (33.7)	0.749	0.80	0.53-1.23	0.318	0.70	0.43-1.13	0.145
≥80y	66/109 (60.6)	61/94 (64.9)	0.563	0.82	0.47-1.46	0.504	0.62	0.31-1.23	0.172
Moderate-severe basal ganglia PVS(>10)									
<60y	4/22 (18.2)	18/142 (12.7)	0.502	1.19	0.35-4.03	0.785	1.07	0.29-3.95	0.920
60-79y	78/253 (30.8)	79/220 (35.9)	0.282	0.61	0.41-0.93	0.020	0.60	0.38-0.95	0.029
≥80y	96/155 (61.9)	31/48 (64.6)	0.865	0.92	0.46-1.82	0.800	0.77	0.33-1.76	0.531
Lacunes									
<60y	5/24 (20.8)	17/140 (12.1)	0.502	1.09	1.01-1.17	0.472	1.39	0.40-4.77	0.606
60-79y	36/88 (40.9)	121/385 (31.4)	0.282	0.90	0.56-1.44	0.666	1.62	0.94-2.82	0.085
≥80y	31/49 (63.3)	96/154 (62.3)	0.865	1.03	0.53-2.02	0.915	0.63	0.30-1.33	0.222

SVD=small vessel disease, WMH=white matter hyperintensity, PVS= perivascular spaces, OR=odds ratio, CI=confidence interval; *Model I: adjusted for age, gender; **Model II: adjusted for age, gender, history of hypertension, diabetes and premorbid mean systolic blood pressure. . Renal impairment is defined as eGFR<60 mL/min/1.73m^2