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Renal Impairment and Risk of Acute Stroke: The INTERSTROKE Study

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Keywords
Kidney disease · Stroke

Abstract
Background: Previous studies reported an association of renal impairment with stroke, but there are uncertainties underpinning this association. ***Aims:*** We explored if the association is explained by shared risk factors or is independent and whether there are regional or stroke subtype variations. ***Methods:*** INTERSTROKE is a case-control study and the largest international study of risk factors for first acute stroke, completed in 27 countries. We included individuals with available serum creatinine values and calculated estimated

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glomerular filtration rate (eGFR). Renal impairment was defined as eGFR <60 mL/min/1.73 m^2. Multivariable conditional logistic regression was used to determine the association of renal function with stroke. ***Results:*** Of 21,127 participants, 41.0% were female, the mean age was 62.3 ± 13.4 years, and the mean eGFR was 79.9 ± 23.5 mL/min/1.73 m^2. The prevalence of renal impairment was higher in cases (22.9% vs. 17.7%, $p < 0.001$) and differed by region ($p < 0.001$). After adjustment, lower eGFR was associated with increased odds of stroke. Renal impairment was associated with increased odds of all stroke (OR 1.35; 95% CI: 1.24–1.47), with higher odds for intracerebral hemorrhage (OR 1.60; 95% CI: 1.35–1.89) than ischemic stroke (OR 1.29; 95% CI: 1.17–1.42) ($p_{\text{interaction}}$ 0.12). The largest magnitudes of association were seen in younger participants and those living in Africa, South Asia, or South America ($p_{\text{interaction}} < 0.001$ for all stroke). Renal impairment was also associated with poorer clinical outcome (RRR 2.97; 95% CI: 2.50–3.54 for death within 1 month). ***Conclusion:*** Renal impairment is an important risk factor for stroke, particularly in younger patients, and is associated with more severe stroke and worse outcomes.

Introduction

Stroke is a leading global cause of death and disability [1, 2], and chronic kidney disease (CKD) is the third fastest growing cause of premature mortality [3]. The INTERSTROKE study reported that ten modifiable risk factors are associated with approximately 90% of the population attributable risk of stroke, with important regional variations, but laboratory measures of renal function were not included [4]. Cardiovascular disease (CVD) is more common with established renal impairment, which itself is an independent risk factor for recurrent CVD and death [5]. In addition, those with CKD are more likely to die from CVD rather than progress to advanced CKD, where renal replacement therapy is required [6].

Stroke and renal impairment share many risk factors (particularly hypertension and diabetes [7]), and key shared risk factors may become amplified in CKD, particularly hypertension. Cardiovascular prevention guidelines recommend screening for CKD in those with atherosclerosis or established CVD [8]. CKD or renal impairment is also a risk factor for stroke, based on systematic reviews and meta-analyses, with increasing risk of stroke as renal function decreases [9–11]. However, these meta-analyses reported moderate-high heterogeneity and the majority of studies were completed in Japan, Europe, and the USA. In addition, it remains unclear if the association is driven by shared risk factors or independent and if there are important regional variations.

Aims

The INTERSTROKE study is ideally placed to explore the global association between renal impairment and stroke to guide stroke prevention strategies. The INTERSTROKE study also allows exploration for regional variations in the prevalence and importance of renal impairment as a risk factor for stroke.

Methods

The design and methodology of the INTERSTROKE study have been previously described in detail [4, 12]. In brief, cases of acute first stroke were recruited (within 5 days of symptom onset and 72 h of hospital admission) from 142 centers in 32 countries. Neuroimaging was performed within 1 week of presentation in 99.9% of participants. Community- or hospital-based controls (without acute stroke) were matched for sex and age (±5 years); matching for age was extended (±10 years) for participants aged >90 years. The study was approved by local ethics committees at all recruitment sites, and all participants (or their proxies) provided written informed consent.

Structured questionnaires and physical examinations were completed in a standardized fashion. Diabetes was defined by self-report of a history of diabetes or HbA1c ≥6.5%. Hypertension was defined by self-report of a history of hypertension or elevated blood pressure (BP) or a measured BP ≥140/90 mm Hg. Physical activity was dichotomized into inactive or mainly active (≥4-h regular moderate/strenuous leisure activity per week). Waist-to-hip ratio (WHR) was categorized into gender-specific tertiles. Diet quality was measured using the modified Alternative Healthy Eating Index (mAHEI) [13, 14]. Smoking was dichotomized as never/former versus current. CVD was defined by a medical history of angina, myocardial infarction, transient ischemic attack, or peripheral arterial disease. All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada, for quality-control checks and statistical analysis. Within 72 h of recruitment, nonfasting blood samples were taken, centrifuged, aliquoted, and frozen to −20 or −70°C before being couriered (nitrogen vapor tanks) to blood storage sites (Canada, India, Turkey, and China) for storage at −160°C. Serum creatinine was measured (in 78.4% [n = 21,127] of INTERSTROKE participants) using the modified Jaffé method on the Beckman Coulter UniCel DxC 600 Synchron Clinical System, where change in absorbance level of a creatinine-picrate complex is proportional to the concentration of creatinine in the serum sample. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to estimate glomerular filtration rate (eGFR) with values truncated at 15 and 90 mL/min/1.73 m [15]. Renal impairment was defined as CKD-EPI eGFR <60 mL/min/1.73 m^2, consistent with the classification of

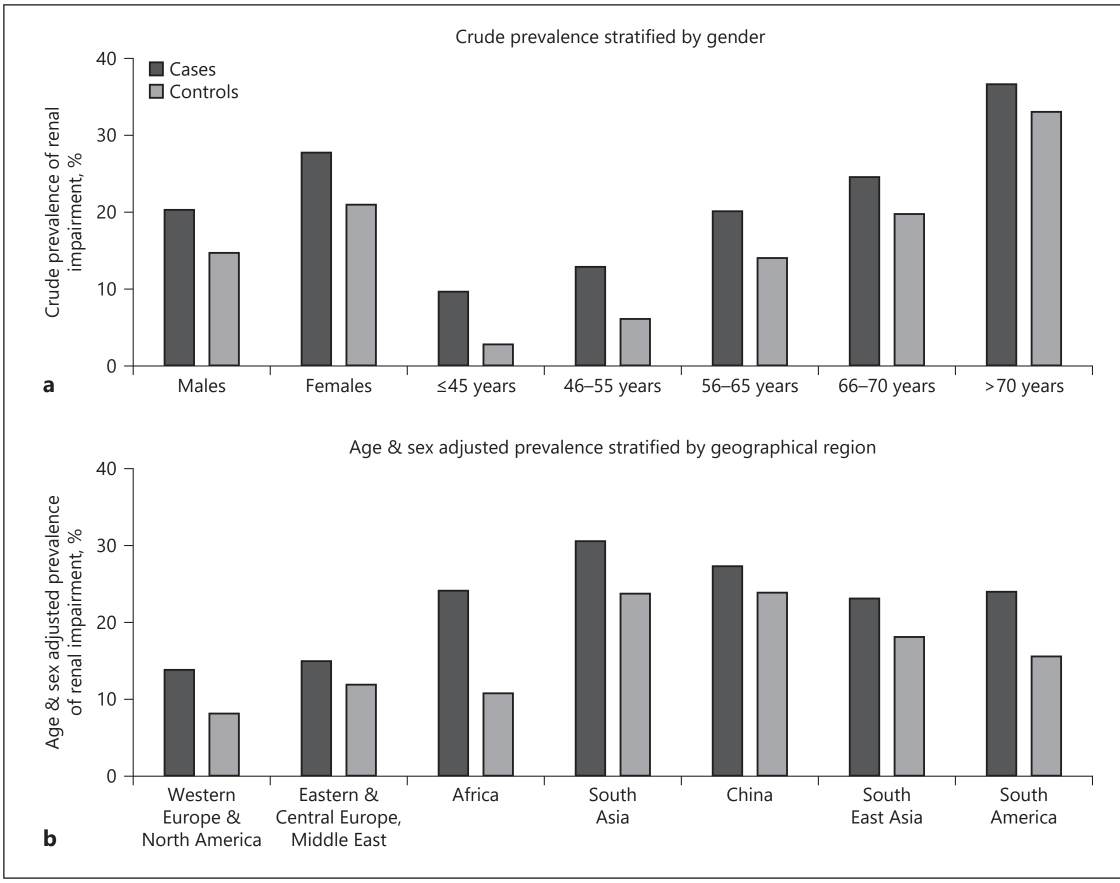

Fig. 1. Prevalence of renal impairment in cases and in controls by age and gender (**a**), and geographical region (**b**).

CKD [16]. In cases, there was no difference in age- and sex-adjusted prevalence of renal impairment when stratified by time between symptom onset and blood draw (<24 h, 23.9%; 24–48 h, 22.7%; 48–72 h, 23.1%; 72–96 h, 23.0%; and >96 h, 23.6%, p_{trend} 0.87).

Descriptive statistics were used to summarize the frequency, proportion, mean, or median compared with *t* tests, χ^2 test, or appropriate nonparametric tests (e.g., Kruskal-Wallis). The prevalence of renal impairment is reported by age group (≤45, 46–55, 56–65, 66–70, and >70 years) and gender, with age- and sex-adjusted prevalence by geographical region (Western Europe and North America, Eastern and Central Europe and Middle East, Africa, South Asia, China, South East Asia, and South America).

Restricted cubic splines (three knots for eGFR) and a Wald-type test for nonlinearity beyond the first knot were used to explore and test for non-linear associations between eGFR and stroke [17] based on multivariable-adjusted conditional logistic regression with prespecified covariates [18, 19] of age, adjusted systolic BP, adjusted diastolic BP, diabetes, physical activity, WHR, diet, and smoking. BP in cases was adjusted for changes in BP related to acute stroke, as described previously [4].

Multivariable-adjusted conditional logistic regression was also used to explore the association between stroke and renal impairment or levels of renal function (eGFR >90, 60–90, 30–60, and <30), reporting odds ratios (OR) and 95% confidence intervals (CI), built in a stepwise fashion; (i) unadjusted; (ii) adding age; (iii) adding lifestyle factors (physical activity, WHR, mAHEI score, and smoking); (iv) adding adjusted BP; and (v) adding diabetes. Models are presented for all stroke, ischemic stroke, and intracerebral hemorrhage (ICH). Ischemic stroke was also stratified by subtype (cardioembolic, large vessel, small vessel, or other [20]). Unconditional adjusted logistic regression models were used for pre-specified subgroup analyses, with additional adjustment for sex and country, with stratification by gender, age, education, hypertension, diabetes, aspirin use, ACE/ARB use, diuretic use, other BP medication, lipid-lowering therapy, and geographical region. *p* for interaction was considered statistically significant when <0.01. Adjusted multinomial logistic regression models were used to explore the associations between renal impairment and stroke severity (at presentation and 1 month poststroke) reporting relative risk ratios (95% CI) using controls as the reference category.

Results

Of the 21,127 participants included, 41.0% (n = 8,664) were female, the mean age was 62.3 ± 13.4 years, and the mean CKD-EPI eGFR was 79.9 ± 23.5 mL/min/1.73 m^2. Excluded participants (i.e., those without available serum

Table 1. Characteristics of renal impairment – overall, cases, and controls

	Cases			Controls		
	no impairment (*n* = 8,133)	renal impairment (*n* = 2,477)	*p* value	no impairment (*n* = 8,698)	renal impairment (*n* = 1,819)	*p* value
Age, mean (SD)	60.9 (13.3)	68.9 (12.5)	<0.001	60.1 (13.0)	70.7 (10.9)	<0.001
Gender, % (*n*)						
Male	61.6 (5,009)	51.4 (1,273)	<0.001	60.6 (5,274)	49.9 (907)	<0.001
Female	38.4 (3,124)	48.6 (1,204)		39.4 (3,424)	50.1 (912)	
Physical activity, % (*n*)						
Mainly inactive	88.2 (7,166)	93.5 (2,314)	<0.001	81.2 (7,062)	89.7 (1,631)	<0.001
Mainly active	11.8 (959)	6.5 (162)		18.8 (1,631)	10.3 (187)	
Education, % (*n*)						
None	11.3 (917)	20.1 (497)		7.7 (673)	15.5 (281)	
1–12 years	66.7 (5,428)	65.9 (1,634)	<0.001	57.3 (4,981)	63.0 (1,145)	<0.001
Trade school/university	22.0 (1,786)	14.0 (346)		35.0 (3,043)	21.5 (391)	
Hypertension, % (*n*)	56.5 (4,592)	68.7 (1,702)	<0.001	34.5 (3,000)	51.4 (934)	<0.001
Diabetes, % (*n*)	16.8 (1,365)	20.0 (496)	<0.001	11.6 (1,011)	19.6 (357)	<0.001
Prior cardiovascular disease, % (*n*)	11.0 (898)	13.3 (330)	0.002	5.6 (486)	10.4 (189)	<0.001
Antiplatelet use, % (*n*)	17.5 (1,422)	19.6 (486)	0.015	14.5 (1,263)	19.6 (356)	<0.001
Oral anticoagulant use, % (*n*)	2.1 (173)	2.5 (62)	0.266	1.0 (85)	2.6 (48)	<0.001
ACEi or ARB use, % (*n*)	21.2 (1,722)	27.1 (670)	<0.001	17.3 (1,502)	26.1 (475)	<0.001
Diuretic use, % (*n*)	10.9 (888)	16.9 (418)	<0.001	7.4 (645)	16.1 (292)	<0.001
Other antihypertensive use, % (*n*)	25.3 (2,054)	34.1 (844)	<0.001	18.7 (1,629)	29.1 (530)	<0.001
Analgesic or anti-inflammatory use, % (*n*)	7.0 (570)	6.7 (167)	0.638	7.0 (605)	6.3 (115)	0.322
Adjusted SBP on admission, mm Hg, mean (SD)	136.2 (24.4)	141.5 (26.6)	<0.001	132.1 (18.2)	135.8 (20.0)	<0.001
Adjusted DBP on admission, mm Hg, mean (SD)	79.1 (14.1)	79.9 (15.4)	<0.001	80.0 (10.6)	79.9 (11.2)	0.002
Waist-to-hip ratio, mean (SD)	0.93 (0.08)	0.93 (0.08)	0.20	0.92 (0.08)	0.92 (0.08)	0.483
mAHEI score, mean (SD)	22.8 (6.4)	22.3 (6.1)	0.002	24.3 (6.8)	22.9 (6.3)	<0.001
HbA1c, mean (SD)	0.0605 (0.013)	0.0617 (0.014)	0.004	0.058 (0.01)	0.060 (0.011)	0.281
eGFR, mean (SD)	88.6 (17.1)	44.7 (13.1)	<0.001	88.6 (16.7)	47.7 (11.0)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; mAHEI, modified Alternative Healthy Eating Index; eGFR, estimated glomerular filtration rate.

creatinine) were more likely to be younger, from South Asia, and with lower levels of education, but were less likely to have hypertension, CVD, or be taking antihypertensive medications (see online suppl. Table 1; see www.karger.com/doi/10.1159/000515239 for all online suppl. material).

Overall, the prevalence of renal impairment was 20.3% ($n = 4,296$), with a higher prevalence in cases (22.9%, $n = 2,476$) than controls (17.7%, $n = 1,823$) ($p < 0.001$), consistent on stratification by gender and age (Fig. 1a). The age- and sex-adjusted prevalence was highest in South Asia and China and lowest in Western Europe and North America, with higher prevalence in cases than controls in all regions (Fig. 1b). Participants with renal impairment were more likely to have hypertension, diabetes, and CVD and to use antiplatelet or antihypertensive medications (Table 1). Predictors of renal impairment included age, gender, physical activity, hypertension, diabetes, medication use, and diet quality, with regional differences (online suppl. Table 2).

Cubic splines showed that lower eGFR was associated with a curvilinear increase in odds of all stroke, ischemic stroke, and ICH (Fig. 2a), which remained significant after multivariable adjustment (Fig. 2b). On multivariable analyses, renal impairment was associated with increased odds of all stroke (OR 1.35; 95% CI: 1.24–1.47), ischemic stroke (OR 1.29; 95% CI: 1.17–1.42), and ICH (OR 1.60; 95% CI: 1.35–1.89) (Table 2). Estimates from conditional and unconditional analyses using model 5 did not alter findings. Patterns of association were consistent within ischemic stroke subtypes (Table 2).

For all stroke, the largest magnitudes of association were seen in younger participants, without diabetes, not using diuretics, and living in Africa, South Asia, or South America (Table 3). For ischemic stroke, the largest magnitudes of association were seen in younger participants,

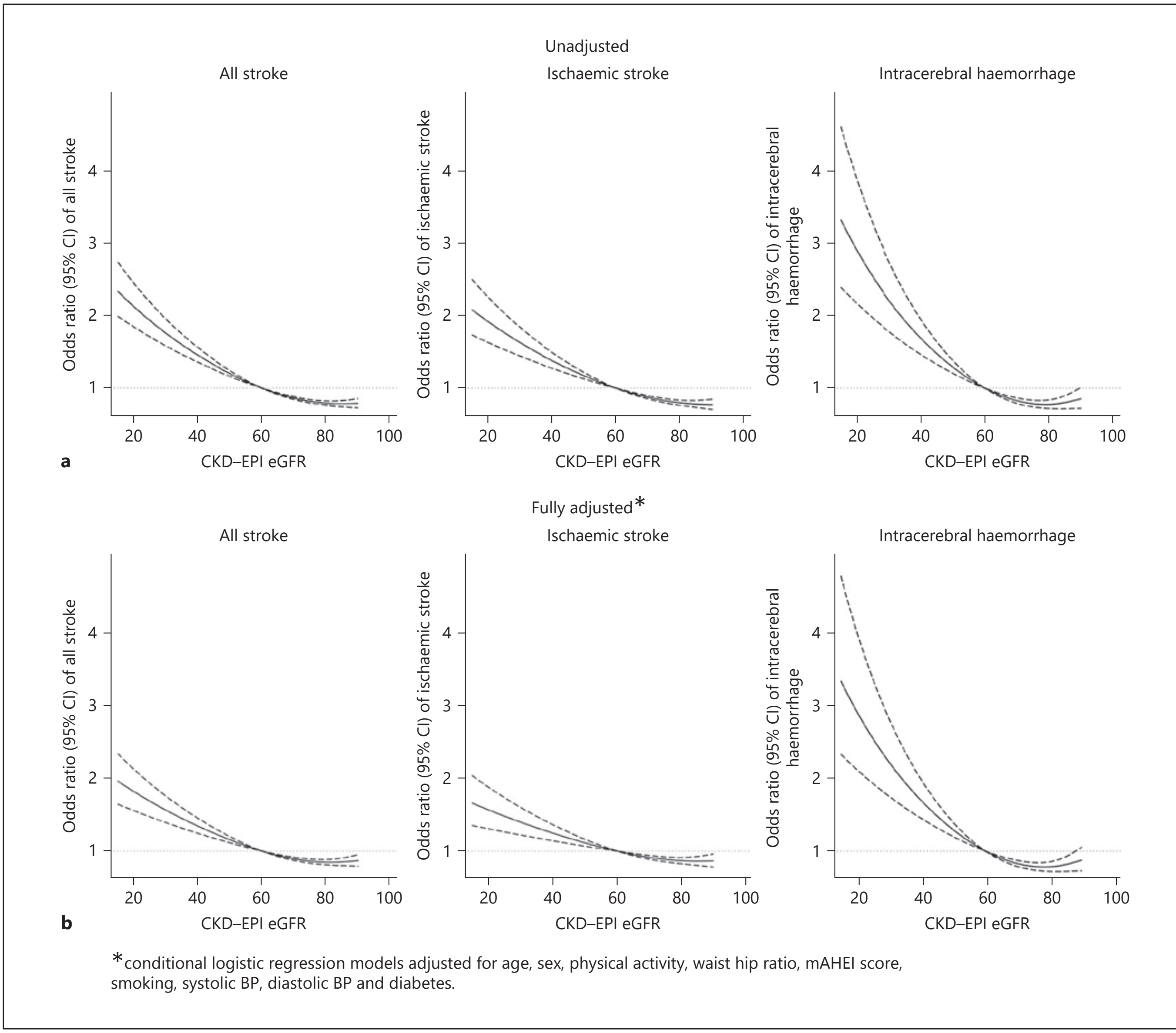

Fig. 2. Association between eGFR and stroke using unadjusted models (**a**) and fully adjusted models (**b**) including age, sex, physical activity, WHR, mAHEI, smoking, systolic BP, diastolic BP and diabetes. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mAHEI, modified Alternative Healthy Eating Index; BP, blood pressure.

without diabetes and in those not using diuretics. For ICH, the largest magnitudes of association were seen in male, younger participants, with highest level of education and living in South Asia, South America, Africa, and South East Asia. There were no other significant differences by subgroup.

With participants stratified by categories of eGFR, consistent associations were seen on both unadjusted and adjusted analyses for all stroke, ischemic stroke, and ICH. Compared to eGFR>90, there was a dose response with the greatest magnitudes of association with the lowest level of eGFR (<30) for all stroke (OR 2.28; 95% CI: 1.80–2.89), ischemic stroke (OR 1.81; 95% CI: 1.37–2.40), and ICH (OR 4.12; 95% CI: 2.59–6.55) (Table 4).

The age- and sex-adjusted prevalence of renal impairment was greatest with higher modified Rankin score on presentation with all stroke, ischemic stroke, and ICH (online suppl. Fig. 1). At presentation, the greatest mag-

Table 2. Association between renal impairment and stroke

	All stroke odds ratio (95% CI)	Ischemic stroke odds ratio (95% CI)	ICH odds ratio (95% CI)	$p_{interaction}$
Model 1	1.52 (1.41–1.64)	1.49 (1.37–1.63)	1.62 (1.39–1.90)	0.37
Model 2	1.45 (1.35–1.57)	1.41 (1.29–1.54)	1.60 (1.37–1.88)	0.16
Model 3	1.41 (1.30–1.52)	1.36 (1.23–1.49)	1.57 (1.33–1.84)	0.12
Model 4	1.38 (1.26–1.50)	1.33 (1.21–1.47)	1.58 (1.34–1.88)	0.17
Model 5	1.35 (1.24–1.47)	1.29 (1.17–1.42)	1.60 (1.35–1.89)	0.12
Ischemic subtypes *				
Cardioembolic stroke	–	1.53 (1.17–2.02)	–	–
Large vessel stroke	–	1.31 (1.04–1.65)	–	–
Small vessel stroke	–	1.29 (1.10–1.52)	–	–
Other TOAST stroke	–	1.50 (1.05–2.13)	–	–
Undetermined TOAST stroke	–	1.06 (0.85–1.31)	–	–

Conditional logistic regression: model 1: unadjusted; model 2: adding age; model 3: adding physical activity, waist-to-hip ratio, mAHEI score, and smoking; model 4: adding systolic and diastolic BP; model 5: adding diabetes. ICH, intracerebral hemorrhage; mAHEI, modified Alternative Healthy Eating Index; BP, blood pressure.
* Using model 5.

nitudes of association were seen between renal impairment and severe or very severe disability (online suppl. Table 1). At 1 month poststroke, the greatest magnitudes of association were seen between renal impairment and death for all stroke (RRR 2.97; 95% CI: 2.50–3.54), ischemic stroke (RRR 2.27; 95% CI: 1.78–2.90), and ICH (RRR 3.63; 95% CI: 2.73–4.83). Thrombolysis was not an effect modifier of the association between renal impairment and stroke outcome ($p_{interaction}$ 0.36).

Discussion

In this large international study, we found a curvilinear monotonic association of reducing eGFR with increased risk of stroke, both for ischemic stroke and ICH. The magnitude of association was larger for ICH, in younger participants and in those living in Africa, South America, and South Asia. By including representation from regions poorly represented previously, we were able to extend previous knowledge to highlight regional differences. Renal impairment was associated with more severe stroke and higher 1-month mortality, even after adjusting for baseline stroke severity.

Our analyses are consistent with previous reports that renal impairment is independently associated with an increased risk of stroke [9], but provides novel information on the association by stroke subtype, demonstrating higher odds for ICH than ischemic stroke and a consistent pattern of association by ischemic stroke subtypes. We did suspect a stronger magnitude of association of renal impairment with stroke subtypes known to have the strongest association with hypertension, which was the case for ICH, but an expected stronger association for small vessel ischemic stroke was not evident in our analyses. This difference may have been observed as renal impairment is closely associated with hypertension, which is a direct risk factor for ICH, but hypertension indirectly impacts small vessel disease through contributions to atherosclerosis. Another contrasting feature by primary stroke subtype was a lower attenuation in OR with the sequential addition of other vascular risk factors (e.g., hypertension and diabetes) for ICH (OR: 1.62 on univariable and 1.60 on full multivariable) than ischemic stroke (OR: 1.49 on univariable and 1.29 on full multivariable). These findings support the contention that renal impairment is more likely to play a causal role in risk of ICH than ischemic, or more linked in mechanism of disease.

The kidney and brain microvascular beds are similarly composed of small, short vessels that arise from large arteries with high pressure ("strain vessels") and with low arterial resistance, which are vulnerable to a number of shared risk factors. Both beds have continuous blood flow maintained by using myogenic regulatory systems, which protects these beds from large changes in blood flow (autoregulation) [21–23]. Failure of these systems may lead to microvessel damage [24] and clinical consequences such as renal impairment or stroke. The complications of renal impairment (anemia, acidosis, uremia, altered calcium-phosphate metabolism, and platelet dysfunction [25]) may lead

Table 3. Stratified analyses of adjusted* association between renal impairment and stroke

	All stroke		Ischemic stroke		ICH	
	odds ratio (95% CI)	$p_{interaction}$	odds ratio (95% CI)	$p_{interaction}$	odds ratio (95% CI)	$p_{interaction}$
Gender						
Male	1.36 (1.23–1.51)	0.28	1.24 (1.10–1.40)	0.96	1.79 (1.44–2.23)	0.006
Female	1.31 (1.17–1.46)		1.31 (1.15–1.48)		1.20 (0.95–1.51)	
Age						
≤45 years	3.36 (2.20–5.11)	<0.001	2.28 (1.32–3.94)	0.003	6.74 (3.21–14.18)	<0.001
46–55 years	2.02 (1.59–2.55)		1.63 (1.20–2.21)		2.69 (1.80–4.01)	
56–65 years	1.55 (1.34–1.81)		1.49 (1.25–1.79)		1.68 (1.24–2.27)	
66–70 years	1.20 (0.98–1.46)		1.20 (0.95–1.51)		1.24 (0.78–1.96)	
>70 years	1.04 (0.93–1.16)		1.07 (0.95–1.21)		0.83 (0.62–1.11)	
Education						
None	1.21 (1.00–1.47)	0.47	1.07 (0.86–1.34)	0.68	1.61 (1.03–2.49)	0.007
1–12 years	1.34 (1.22–1.47)		1.34 (1.20–1.50)		1.30 (1.07–1.58)	
Trade school / university	1.32 (1.10–1.57)		1.11 (0.91–1.36)		2.63 (1.72–4.01)	
Hypertension						
No	1.24 (1.07–1.44)	0.13	1.24 (1.05–1.47)	0.14	1.20 (0.85–1.69)	0.65
Yes	1.29 (1.18–1.41)		1.20 (1.08–1.34)		1.54 (1.26–1.87)	
Diabetes						
No	1.40 (1.28–1.53)	0.003	1.35 (1.22–1.50)	0.001	1.49 (1.24–1.77)	0.64
Yes	1.20 (1.04–1.39)		1.10 (0.94–1.29)		1.56 (1.07–2.27)	
Aspirin						
No	1.34 (1.24–1.46)	0.06	1.28 (1.16–1.41)	0.13	1.48 (1.26–1.75)	0.36
Yes	1.26 (1.06–1.51)		1.20 (0.99–1.46)		1.62 (0.90–2.90)	
ACEi/ARB						
No	1.34 (1.22–1.46)	0.03	1.26 (1.13–1.39)	0.10	1.50 (1.26–1.78)	0.24
Yes	1.31 (1.13–1.52)		1.28 (1.08–1.51)		1.45 (0.97–2.17)	
Diuretics						
No	1.38 (1.27–1.49)	<0.001	1.31 (1.19–1.44)	0.003	1.50 (1.27–1.77)	0.39
Yes	1.12 (0.92–1.38)		1.05 (0.84–1.31)		1.40 (0.74–2.65)	
Other BP medications						
No	1.32 (1.20–1.44)	0.09	1.28 (1.15–1.42)	0.03	1.37 (1.14–1.64)	0.34
Yes	1.33 (1.16–1.53)		1.20 (1.03–1.41)		2.02 (1.43–2.86)	
Lipid-lowering therapy						
No	1.34 (1.24–1.45)	0.32	1.26 (1.15–1.39)	0.58	1.53 (1.30–1.81)	0.30
Yes	1.27 (1.04–1.56)		1.27 (1.02–1.58)		0.90 (0.39–2.08)	
Geographical region						
Western Europe + North America	1.36 (1.09–1.69)	<0.001	1.39 (1.10–1.75)	0.12	0.81 (0.30–2.21)	<0.001
Eastern + Central Europe + Middle East	1.10 (0.86–1.40)		1.09 (0.84–1.41)		1.40 (0.51–3.84)	
Africa	2.32 (1.72–3.12)		2.30 (1.56–3.40)		2.21 (1.33–3.69)	
South Asia	1.86 (1.40–2.45)		1.42 (1.01–2.00)		3.91 (1.94–7.80)	
China	1.15 (1.03–1.29)		1.20 (1.05–1.38)		1.02 (0.82–1.27)	
South East Asia	1.33 (1.01–1.75)		1.09 (0.77–1.53)		1.87 (1.14–3.06)	
South America	1.49 (1.22–1.82)		1.19 (0.94–1.51)		3.08 (1.96–4.85)	

Unconditional logistic regression including adjustment for age, sex, systolic BP, diastolic BP, diabetes, physical activity, waist-to-hip ratio, mAHEI score, smoking, and country. ICH, intracerebral hemorrhage; mAHEI, modified Alternative Healthy Eating Index; BP, blood pressure.

to vascular calcification, endothelial dysfunction [26], and decreased cerebral perfusion, promoting tissue hypoxia [27] and worsening stroke outcome [28]. Renal impairment is also associated with worsening hypertension (which is part of the causal pathway for CVD), platelet dysfunction, and prolonged bleeding time [29], which may explain the increased risk of ICH. These postulated mechanisms are consistent with our findings which confirm previous reports that the magnitude of association was largest between renal impairment and fatal stroke [9, 30].

Table 4. Graded association between categories of CKD-EPI eGFR and stroke

	Prevalence, % (*n*)	Model 1 – unadjusted, OR (95% CI)	Model 2 – age, OR (95% CI)	Model 3 – lifestyle, OR (95% CI)	Model 4 – BP, OR (95% CI)	Model 5 – diabetes, OR (95% CI)
All stroke						
eGFR>90	35.0 (3,718)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
eGFR 60–90	41.6 (4,415)	1.08 (1.01–1.17)	1.02 (0.94–1.10)	1.02 (0.94–1.11)	1.03 (0.95–1.12)	1.03 (0.95–1.12)
eGFR 30–60	20.1 (2,132)	1.50 (1.36–1.65)	1.37 (1.24–1.52)	1.33 (1.20–1.48)	1.32 (1.18–1.46)	1.29 (1.16–1.44)
eGFR<30	3.3 (345)	2.88 (2.33–3.57)	2.57 (2.06–3.21)	2.51 (1.99–3.16)	2.37 (1.87–2.99)	2.28 (1.80–2.89)
Ischemic stroke						
eGFR>90	34.8 (2,881)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
GFR 60–90	42.3 (3,501)	1.07 (0.99–1.17)	1.00 (0.92–1.10)	1.00 (0.92–1.10)	1.00 (0.91–1.10)	1.00 (0.91–1.10)
eGFR 30–60	20.2 (1,670)	1.50 (1.34–1.67)	1.35 (1.20–1.51)	1.30 (1.15–1.47)	1.28 (1.13–1.45)	1.25 (1.10–1.41)
eGFR<30	2.8 (228)	2.45 (1.91–3.14)	2.13 (1.64–2.75)	2.04 (1.56–2.68)	1.94 (1.47–2.56)	1.81 (1.37–2.40)
Intracerebral hemorrhage						
eGFR>90	35.9 (837)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
eGFR 60–90	39.2 (914)	1.12 (0.96–1.30)	1.05 (0.90–1.23)	1.07 (0.91–1.26)	1.11 (0.94–1.31)	1.11 (0.93–1.31)
eGFR 30–60	19.8 (462)	1.50 (1.23–1.82)	1.43 (1.17–1.74)	1.42 (1.15–1.74)	1.48 (1.19–1.84)	1.49 (1.20–1.84)
eGFR<30	5.0 (117)	4.44 (2.88–6.85)	4.16 (2.68–6.45)	4.05 (2.60–6.31)	4.05 (2.55–6.43)	4.12 (2.59–6.55)

Conditional logistic regression. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; BP, blood pressure.

Renal impairment was a stronger risk factor in younger populations, potentially reflective of more significant hypertension or renal pathology, and in lower income regions, where CKD and associated complications such as hypertension may be less likely to be recognized and treated. These observations suggest an important role of renal impairment as a potential target for reducing the burden of premature stroke. Our study includes populations from geographical regions poorly represented in previous studies and demonstrates significant regional variation in the association between renal impairment and stroke, particularly for ICH [9]. While we report a significant association of renal impairment with stroke in almost all regions, the magnitude of association differed, with largest odds in South Asia and Africa. This may reflect underrecognition of renal impairment or CKD in these regions or differences in the pathology causing renal impairment. Prior meta-analyses reported the largest magnitude of association in those of Asian ethnicity [9], but these may not have adequately adjusted for the modifying effect of hypertension [11].

The association between renal impairment and stroke outcome at 1 month is consistent with previous reports [31], as well as other reports with longer follow-up [32–36]. In addition, we confirm previous reports of a dose-response association between stroke and strata of eGFR [37, 38]. Mean eGFR was lower in those with more severe stroke at presentation and at 1 month post-stroke (online suppl. Table 3). Although other studies report that renal impairment is associated with poor outcomes in those who received thrombolysis [39, 40], we found no significant difference, although the proportion that received thrombolysis was low (7.8% of ischemic stroke).

Our study has a few limitations. First, as we used a case-control approach, it is possible that the measurement of eGFR could be affected by hemodynamic changes associated with acute stroke. A previous prospective cohort study of patients hospitalized with first stroke reported no association between the mean time delay to hospital admission and eGFR [41]. Consistent with this report, we found no difference in the age- and sex-adjusted prevalence of renal impairment when participants were stratified by the duration between symptom onset and the time of blood draw. In addition, as renal function is estimated using objective, laboratory methodologies and CKD-EPI eGFR was calculated centrally, there is less likelihood of differential assessment in cases and controls. Second, we had no information on renal function prior to stroke or measurement of proteinuria or albuminuria, and as such we cannot distinguish acute reductions in renal function from chronic kidney disease or from intra-individual fluctuations. However, previous studies report stronger associations between eGFR and stroke, rather than proteinuria [9–11]. Third, these analyses are observational and cannot establish a causative relationship or may be influenced by residual confounding. Fourth, it is possible that our findings may be affected by reverse causation, in which those presenting with acute stroke are more likely to have reduced eGFR. However, our finding that the prevalence of renal impairment was consistent when stratified by length of time from symptom onset to blood draw argues against this, where severity of illness may be more likely to increase renal impairment.

The main strength of our study is the large number of stroke cases and controls, including representation from all geographical regions. Although this is a case-control study of stroke precluding estimates of stroke prevalence, it does allow us to estimate prevalence of renal impairment. Second, all strokes underwent detailed assessment including radiological assessment and classification, facilitating exploration of the association between renal impairment and stroke types. This is particularly important as although CKD and CVD share many risk factors, our study shows the strongest association between renal impairment and ICH, where hypertension is a key risk factor. Third, the sampling approach included a combination of hospital- and community-based controls, increasing the generalizability of our findings. Fourth, our analytic approach, including a range of different approaches and subgroup analyses, yielded robust results.

Conclusion

In this large international study, we found a curvilinear association between reducing eGFR and increasing risk of all stroke, ischemic stroke, and ICH. We report higher odds for ICH than ischemic stroke and similar patterns of association by ischemic stroke subtype. This highlights that renal impairment is a potential risk factor for stroke, further enforcing the importance of management of hypertension and other risk factors (i.e., the cornerstone of CKD management). In addition, renal impairment may need to be considered in primary prevention strategies for stroke, particularly for anticoagulation strategies and considering the risk of ICH.

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Statement of Ethics

The INTERSTROKE study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was approved by local ethics committees at all recruitment sites, and all participants (or their proxies) provided written informed consent before inclusion in the study.

Conflict of Interest Statement

G.J.H. reports personal fees from Bayer and Medscape, outside of this work. All other authors have no disclosures and declare no conflicts of interest.

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Author Contributions

M.O.D. and S.Y. designed the INTESTROKE study; S.R. and S.L.C. managed and operationally led the study; X.W., F.A.W., A.Y., A.E., A.D., A.A., A.C., A.R., A.L.D., A.O., C.M., C.W., D.R., D.X., F.L., G.M., G.J.H., H.K.I., H.Z., K.Y., N.P., P.L.J., P.L., R.D., and S.O. recruited patients into the study. A.S., C.J., G.P., M.C., and M.O.D. designed these analyses; A.S. analyzed the data, made the figures, and drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

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