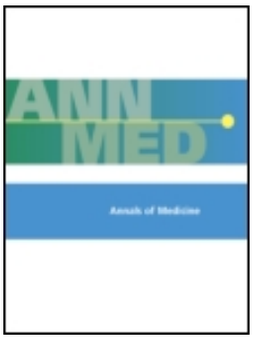

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ORIGINAL ARTICLE

Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population

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Abstract

Aims. The association between chronic kidney disease (CKD) and different subtypes of stroke is unclear, and previous studies have yielded conflicting results. We aimed to assess the impact of CKD on the risk of fatal or non-fatal ischemic and hemorrhagic stroke in both men and women.

Methods. In 539,287 Swedish men and women, mainly undergoing health controls, with mean age 45 years, and no previous stroke or myocardial infarction, hazard ratios for stroke were calculated to assess the association between renal dysfunction and incidence of stroke. We estimated glomerular filtration rates (GFR) using the Mayo (GFR-Mayo) formula. Glomerular filtration rate 60–90, 30–60, and 15–30 mL per minute per 1.73 m^2 was defined as mildly, moderately, and severely decreased GFR, respectively.

Results. There were 17,678 strokes, of which 72% were ischemic, 15% hemorrhagic, and 12% unspecified, during 12 years of follow-up. Hazard ratios (95% confidence intervals) for ischemic stroke were 1.09 (1.04–1.14) for mildly, 1.24 (1.10–1.39) for moderately, and 2.27 (1.63–3.17) for severely decreased GFR-Mayo. The corresponding figures for hemorrhagic stroke were 1.04 (0.93–1.15), 1.26 (0.96–1.64), and 2.31 (1.10–4.87). Ischemic stroke was related to all levels of decreased GFR-Mayo in both genders ($P < 0.0003$). Hemorrhagic stroke was only related to renal dysfunction among women; hazard ratios (95% confidence intervals) 1.38 (1.14–1.66) for mildly, 1.70 (1.13–2.57) for moderately, and 3.46 (1.09–10.9) for severely decreased GFR-Mayo.

Conclusions. Already mildly decreased GFR-Mayo increases the risk of ischemic fatal or non-fatal stroke and severely decreased GFR-Mayo the risk of hemorrhagic stroke in the general population. In gender-specific analyses ischemic stroke was related to a decreased GFR-Mayo in both genders. Hemorrhagic stroke was only related to renal dysfunction among women.

Key words: *Cerebrovascular disease, epidemiology, kidney disease, risk factors, stroke*

Introduction

Cerebrovascular disease is the second leading cause of death globally, accounting for 10% of all deaths (1). A large proportion of all ischemic strokes may be causally attributed to hypertension, dyslipidemia, carotid artery stenosis, and atrial fibrillation (2). Other established risk factors for stroke are cigarette smoking, diabetes mellitus, and valvular and coronary heart disease (3).

Chronic kidney disease (CKD) is prevalent and affects approximately 10% of the adult population

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Key messages

- Kidney dysfunction predicts both ischemic and hemorrhagic fatal and non-fatal stroke in a previously healthy middle-aged cohort.
- Only women were found to have an increased risk of fatal or non-fatal hemorrhagic stroke in gender-specific analyses.

(4,5). The presence of CKD increases the risk of all-cause and cardiovascular mortality in both the general population and among the elderly (6,7). In addition CKD is associated with an increased incidence of myocardial infarction in middle-aged populations free of previous cardiovascular disease (8,9). Studies published on the relation between CKD and stroke have shown conflicting results (6,10–16). Three studies have subtyped strokes into ischemic or hemorrhagic (10,12,15). One of these studies found an association between fatal ischemic but not hemorrhagic stroke (15). In another study, fatal or non-fatal ischemic stroke was related to decreased glomerular filtration rates (GFR), but no information about hemorrhagic stroke was reported (12). There is only one previous study that has stratified both fatal or non-fatal stroke into ischemic and hemorrhagic (10). In that study an association with CKD was found only for hemorrhagic stroke. None of these studies reported gender-specific analyses. These conflicting results may depend on relatively small sample sizes and few events during follow-up. Another explanation may be that definitions of renal function have varied, leading to different classifications of renal dysfunction.

The aim of our study was to investigate the association between renal dysfunction and ischemic and hemorrhagic stroke, among previously healthy middle-aged men and women. Also, since information on the risk for stroke, associated with gender and age, among those with renal dysfunction is lacking, we wanted to assess if the impact of renal dysfunction on the risk of stroke differs between men and women and also in relation to different age groups.

Material and methods

Study population

The study subjects were included from the Apolipoprotein MOrtality RISk Study (AMORIS) cohort consisting of 689,714 Swedish men and women who during 1985–1996 were referred for clinical laboratory testing as part of health check-ups or from out-patient clinics mainly in greater Stockholm area, Sweden. The physicians referring the patients decided what laboratory tests would be analyzed from seven predefined panels of tests. The aim of the AMORIS study was originally to study the importance of apolipoproteins B and A-1 as predictors of cardiovascular disease (17). Information on socio-demographic characteristics including socio-economic status and country of birth was collected from Swedish national censuses carried out in 1985 and 1990. A total of 72% of the study population were living in Stockholm County at the census closest to inclusion date; 15% were born in other countries than Sweden, which corresponds to the proportion of foreign-born individuals in Stockholm County in 1990. Less than 1% of the study population were born in black Africa or North America. Social class was divided into three categories: manual workers, lower non-manual employees, and intermediate or high non-manual employees, and there were 41%, 46%, and 23% in each group, respectively. The corresponding figures for Stockholm County in 1990 were 37%, 42%, and 21%. The standardized mortality ratio was 0.86, indicating that the cohort was somewhat healthier than the general population of Stockholm. The AMORIS cohort has been described elsewhere in detail (8,18). No individuals were hospitalized at the time of investigation. All blood samples were analyzed at one laboratory (CALAB Medical Laboratories, Stockholm, Sweden).

All ($n = 539{,}287$) individuals 30 years of age or older, with at least one registered creatinine value, and no previous stroke or myocardial infarction, were included in the present study.

Information on smoking was available in a subgroup of 8,360 women from the Swedish medical birth register. Before inclusion, information on hospitalizations with a discharge diagnosis of stroke or myocardial infarction and other diagnoses (defined according to International Classification of Diseases versions 8, 9, and 10) was obtained from registers of hospital discharges going back to 1964 regionally and 1987 nationally in Sweden. Blood pressure levels or current medications were not known.

The study complies with the Declaration of Helsinki, and it was approved by the Ethics Committee at Karolinska Institutet.

Laboratory methods

Blood samples were drawn after fasting overnight in most subjects: 16% were non-fasting, and 20% had no information on food intake. Concentrations of total cholesterol and triglycerides were analyzed by enzymatic techniques as described previously (17,19). Diabetes mellitus was defined as fasting

serum glucose of more than 7.0 mmol/L (126 mg/dL) or hospitalization before inclusion with diabetes mellitus as discharge diagnosis (Table I). There was no information on presence or absence of proteinuria. All laboratory methods were accredited and performed with automated multichannel instruments with systems for automatic calibration (19).

Renal function

Serum creatinine was analyzed by a non-kinetic alkaline picrate method (Jaffé), using an Auto-Chemist-PRISMA (New Clinicon, Stockholm, Sweden) during 1985–1992 and a DAX-96 analyzer (Technicon Instruments, Tarrytown, NY, USA) during 1993–1996. Coefficients of variation for creatinine determinations were less than 3.1% at 75.5 μmol/L (0.85 mg/dL), 1.7% at 212 μmol/L (2.4 mg/dL), and 1.6% at 547 μmol/L (6.2 mg/dL). Our creatinine values were compared with values from the NHANES 2001–2002 and 2003–2004 surveys, which previously have been found to correspond to standardized creatinine values (4). Mean creatinine among white non-Hispanics in NHANES 2001–2002 and 2003–2004 surveys were 2.6 μmol/L (0.03 mg/dL) lower as compared to those in the AMORIS population. No direct or indirect adjustment of our creatinine values to standardized creatinine was made.

Only 3.2% of the study population had more than one creatinine value reported within 1 year of inclusion. Thus, in most cases the estimation of GFR was based on a single measurement of creatinine. Since creatinine values can change rapidly secondary to acute illness, subjects with one creatinine value differing more than 20% from another ($n = 7{,}878$) within 1 year were scrutinized manually, and the value believed to represent stable kidney function was chosen.

GFR was estimated using the Mayo formula (20): GFR-Mayo = exp (1.911 + (5.249/(serum-creatinine in μmol/L/88.4)) − (2.114/(serum-creatinine in μmol/L/88.4)^2) − 0.00686 × age − 0.205 (only for women)); if serum-creatinine is <71 μmol/L the value 71 is used in the formula. In addition we used the simplified Modification of Diet in Renal Disease study equation to estimate GFR (21): GFR-MDRD = 186 × (serum-creatinine in μmol/L/88.4)$^{-1.154}$ × age$^{-0.203}$; in women the value is multiplied by 0.742. We did not adjust GFR-MDRD for race since less than 1% of our subjects were black. Estimated glomerular filtration rate was expressed in mL/min per 1.73 m^2 body surface area.

Chronic kidney disease was defined as GFR less than 60 mL/min per 1.73 m^2. GFR > 90, and 60–90, 30–60, and <30 mL/min per 1.73 m^2 were defined as normal renal function, and mildly, moderately, and severely decreased GFR, respectively.

Outcomes

The index date was chosen according to concurrent first measurement of serum creatinine, total cholesterol, triglycerides, and glucose. Follow-up started at the index date and ended for stroke at the time of fatal or non-fatal stroke, death from other causes, emigration, or 31 December 2002, whichever came first. The mean follow-up time was 11.8 years.

New cases of stroke were identified from registers of hospital discharges and the Swedish national cause-of-death register. Cerebrovascular disease (CVD) was defined as codes 330–334 in

Table I. Characteristics of study population in relation to glomerular filtration rates estimated by the Mayo formula.

		Estimated GFR (mL/min/1.73 m^2)			
	All	>90	60–90	30–60	15–30
All individuals:	539,418	477,046	59,016	3,006	350
Percent of study population	100	88.4	10.9	0.56	0.07
Age (years)[a]	44.7 (14.2)	42.1 (12.3)	64.5 (11.56)	72.5 (12.2)	67.3 (15.5)
Female sex (%)	46.7	44.5	64.1	49.3	39.1
Diabetes mellitus (%)[b]	3.0	2.5	6.3	14.6	14.6
Estimated GFR (mL/min/1.73 m^2)[a]	109.1 (16.9)	79.4 (11.4)	81.9 (6.8)	50.3 (7.7)	20.8 (6.7)
Laboratory values:					
Glucose (mmol/L)[a]	5.98 (1.26)	4.9 (1.2)	5.4 (1.7)	5.9 (2.7)	67.3 (15.5)
Total cholesterol (mmol/L)[a]	5.57 (1.16)	5.5 (1.1)	6.2 (1.2)	6.2 (1.4)	6.1 (1.6)
Triglycerides (mmol/L)[a]	1.32 (0.98)	1.29 (0.97)	1.53 (1.04)	1.93 (1.26)	2.06 (1.36)
Serum creatinine (μmol/L)[a]	81.2 (14.5)	79.4 (11.4)	91.7 (15.2)	131.1 (19.6)	281.7 (146.0)

To convert total cholesterol to mg/dL, divide by 0.02586; to convert triglycerides to mg/dL divide by 0.01129; to convert glucose to mg/dL divide by 0.05551; and to convert serum creatinine to mg/dL divide by 88.4.

GFR = glomerular filtration rate.

[a]Age, GFR, and all laboratory values are given as means with standard deviations.

[b]Includes individuals with fasting serum glucose >7.0 mmol/L (>126 mg/dL) or prior hospitalization for diabetes.

International Classification of Disease (ICD) 7, codes 430–438 in ICD-8 or ICD-9, and codes I60–I69 in ICD-10. Ischemic stroke was defined as code 332 in ICD-7, codes 432–434 in ICD-8, codes 433–434 in ICD-9, and code I63 in ICD-10. Hemorrhagic stroke was defined as code 331 in ICD-7, code 431 in ICD-8 and ICD-9, and code I61 in ICD-10. During the study period, in general neuroimaging by computed tomography was used in Sweden to diagnose and subtype stroke. Some of the unspecified cases may have been diagnosed solely by clinical signs and symptoms.

A hospital discharge register covering all emergency hospitals in Sweden was available from 1987. From 1964 to 1986, information on hospital discharges was available for certain regions of Sweden, including Stockholm County from 1969, with almost a complete coverage of the whole country in 1985. Cause of death was obtained from the Swedish national cause-of-death register. The validity of the stroke diagnosis in hospitals in the Nordic countries has been investigated in a few studies (22–24). Recent studies have found the sensitivity to be in the order of 80%–85% and the positive predictive value of about 70%–85% (25,26). Information about emigration was collected from the Swedish register of immigration and emigration.

Statistical analysis

Patient characteristics for subjects with different levels of renal function were presented using descriptive statistics. The hazard ratio of all stroke, ischemic or hemorrhagic stroke for subjects with mildly, moderately, and severely decreased GFR, compared to subjects with normal renal function, was estimated crude and in multivariable analysis using Cox's proportional hazards regression. We used multivariable analyses to reduce the influence of confounding in the evaluation of associations between renal dysfunction and outcomes. Estimates of hazard ratios were accompanied by asymptotic 95% confidence intervals. Test of trend across groups of renal function was made by treating group number as an interval scale variable in the Cox regression model.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Role of the funding source

The funding source had no role in the analysis or interpretation of data or in the decision to submit the manuscript for publication.

Results

Patient characteristics

The mean age for women and men were 46 and 45 years, respectively. Normal renal function was present in 88% of the study population (Table I). With increasing degree of renal dysfunction the subjects were more likely to be older, have higher levels of total cholesterol or triglycerides, or a history of diabetes mellitus (Table I).

Stroke

There were in total 17,678 fatal or non-fatal strokes during follow-up. Of these, 12,856 (73%) were defined as ischemic, 2,696 (15%) as hemorrhagic, and 2,126 (12%) were unspecified. Adjusted hazard ratios for all stroke increased for all levels of renal dysfunction (Table II). Ischemic stroke increased already at mildly decreased GFR after adjustment for age, gender, triglycerides, total cholesterol, and diabetes mellitus. The association between renal dysfunction and hemorrhagic stroke was present only for individuals with severe renal dysfunction after adjustment for confounders (Table II).

Gender-specific analyses showed that ischemic stroke was increased already at mild renal dysfunction both among men and women (Table III). Among women, but not among men, there was a graded and strong increase in risk of hemorrhagic stroke with decreasing GFR after adjustment for confounders (Table III).

An increased risk with decreased GFR was present for all, ischemic and hemorrhagic stroke, and renal dysfunction in younger as well as in older individuals (Table IV). The adjusted hazard ratios among younger individuals with moderately or severely decreased GFR were approximately twice those among elderly individuals.

When we used the MDRD study equation to classify renal function in general the association between decreased GFR and stroke was weaker than when using the Mayo formula (Appendix).

Discussion

The results of the present study indicates that renal dysfunction is a predictor of ischemic and hemorrhagic stroke and that already a mild reduction in GFR is associated with ischemic stroke for both genders and also with hemorrhagic stroke in women. Considering that 12% of our study population had GFR below 90 mL/min per 1.73 m^2 using the Mayo formula and that cerebrovascular disease (CVD) is one of the leading causes of death globally, this has potentially important public health implications.

Table II. Hazard ratios of stroke with 95% confidence intervals in relation to glomerular filtration rate estimated by the Mayo formula.

	GFR-Mayo (mL/min/1.73 m^2)				
	>90	60–90	30–60	15–30	Test for trend
Number of subjects	476,955	58,967	3,015	350	
All strokes:					
No. of strokes	10,782	6,299	549	48	
Crude	1.00	5.38 (5.22–5.55)	15.1 (13.9–16.5)	14.4 (10.9–19.2)	$P<0.0001$
Adjustment for age and sex	1.00	1.13 (1.09–1.18)	1.59 (1.45–1.76)	2.31 (1.74–3.08)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.09 (1.05–1.14)	1.43 (1.30–1.57)	2.23 (1.65–2.96)	$P<0.0001$
Ischemic stroke:					
No. of strokes	7,685	4,751	384	36	
Crude	1.00	5.68 (5.48–5.89)	14.9 (13.4–16.5)	15.5 (11.2–21.5)	$P<0.0001$
Adjustment for age and sex	1.00	1.13 (1.08–1.19)	1.43 (1.28–1.59)	2.32 (1.67–3.23)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.09 (1.04–1.14)	1.24 (1.10–1.39)	2.27 (1.63–3.17)	$P<0.0001$
Hemorrhagic stroke:					
No. of strokes	1,782	841	66	7	
Crude	1.00	4.24 (3.91–4.61)	10.5 (8.20–13.4)	12.2 (5.78–25.5)	$P<0.0001$
Adjustment for age and sex	1.00	1.06 (0.95–1.17)	1.35 (1.04–1.75)	2.33 (1.10–4.91)	$P=0.027$
Multivariable adjustment[a]	1.00	1.04 (0.93–1.15)	1.26 (0.96–1.64)	2.31 (1.10–4.87)	$P=0.095$

GFR = glomerular filtration rate.
[a]Multivariable adjustment was made for age, gender, diabetes mellitus, total cholesterol, and triglycerides.

There are few studies published on the association between CKD and stroke, and the results have been conflicting (6,10–15). This may be explained partly by the use of different classifications for renal function. Also, the sample sizes have been relatively small, leading to few events during follow-up.

To our knowledge no previous study has reported gender-specific data on the relationship between renal dysfunction and stroke. Also, there are only three previous studies investigating CKD as a predictor of stroke where stroke has been subtyped into ischemic or hemorrhagic (10,12,15). In one of these studies a relationship was found between reduced GFR and fatal or non-fatal ischemic stroke, but not hemorrhagic stroke (15). In another study both fatal and non-fatal ischemic stroke was related to renal dysfunction (12). However, in that study no results were reported concerning the association between hemorrhagic stroke and decreased GFR. The Rotterdam study reported risk of both fatal and non-fatal ischemic and hemorrhagic stroke in relation to GFR (10). In that study only hemorrhagic stroke was associated with renal dysfunction. In our study we found that, at least in women, both subtypes of stroke were associated with renal dysfunction and that, at least for ischemic stroke, the increase in risk already started among those with mildly decreased GFR in both genders. The association was graded, and individuals with severe renal dysfunction had an approximately 2-fold increased risk for total as well as both subtypes of stroke after adjustment for confounders known to us. One reason for these conflicting results may be differences in the characteristics of study populations. The AMORIS population is a relatively young cohort with a median age of 45 years compared with a median age of 67 years in the Rotterdam study cohort. In addition, there were 61% women in the Rotterdam study cohort compared with 47% in our study population. Thus, since the impact of CKD on risk for hemorrhagic stroke in our study was different among women compared with men and the proportion of women differed considerably between the two populations this may partly explain differences in the findings. In a Taiwanese study they found that ischemic but not hemorrhagic stroke was associated with fatal stroke (15). Since we in our study found the association between a reduced GFR and hemorrhagic stroke to be stronger among women than among men, this may be explained by few women being included in that study cohort. Also, in the Rotterdam study there were relatively few hemorrhagic strokes during follow-up, and even if the finding was statistically significant the confidence intervals were wide and thus the observations imprecise. In addition the associations between stroke and renal dysfunction tended to be weaker among older compared with younger individuals. Notably, multivariable correction for a number of confounders including hypertension and smoking only had a marginal influence on the point estimates of the Rotterdam study. Thus, it is less likely that residual confounding can explain differences in results.

Gender-specific analyses showed that ischemic stroke was related to decreased GFR both among men and women. The hazard ratios increased from

Table III. Gender-specific hazard ratios of stroke with 95% confidence intervals in relation to glomerular filtration rate estimated by the Mayo formula.

	GFR-Mayo (mL/min/1.73 m^2)				
	>90	60–90	30–60	15–30	Test for trend
Men					
All strokes:					
No. of strokes	7,574	2,266	263	22	
Crude	1.00	4.10 (3.91–4.30)	11.1 (9.79–12.5)	8.35 (5.49–12.7)	$P<0.0001$
Adjustment for age	1.00	1.08 (1.03–1.14)	1.51 (1.33–1.72)	1.65 (1.08–2.50)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.05 (1.00–1.11)	1.44 (1.26–1.64)	1.62 (1.05–2.48)	$P<0.0001$
Ischemic stroke:					
No. of strokes	5,502	1,785	186	18	
Crude	1.00	4.43 (4.20–4.67)	10.69 (9.23–12.4)	9.51 (5.99–15.1)	$P<0.0001$
Adjusted for age	1.00	1.12 (1.06–1.19)	1.36 (1.16–1.58)	1.80 (1.13–2.86)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.08 (1.02–1.15)	1.27 (1.08–1.49)	1.86 (1.17–2.96)	$P<0.0001$
Hemorrhagic stroke:					
No. of strokes	1,331	313	33	4	
Crude	1.00	3.14 (2.78–3.55)	7.67 (5.43–10.83)	8.50 (3.19–22.6)	$P<0.0001$
Adjustment for age	1.00	0.91 (0.80–1.04)	1.21 (0.85–1.73)	1.98 (0.74–5.28)	$P=0.75$
Multivariable adjustment[a]	1.00	0.88 (0.77–1.01)	1.16 (0.80–1.68)	1.98 (0.74–5.31)	$P=0.47$
Women					
All strokes:					
No. of strokes	3,208	4,033	286	26	
Crude	1.00	8.20 (7.83–8.59)	24.3 (21.5–27.4)	31.3 (21.3–46.1)	$P<0.0001$
Adjustment for age	1.00	1.24 (1.16–1.33)	1.80 (1.57–2.07)	3.71 (2.51–5.49)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.20 (1.12–1.28)	1.51 (1.31–1.74)	3.23 (2.17–4.82)	$P<0.0001$
Ischemic stroke:					
No. of strokes	2,183	2,966	198	18	
Crude	1.00	8.86 (8.39–9.37)	25.1 (21.7–29.0)	33.0 (20.8–52.4)	$P<0.0001$
Adjusted for age	1.00	1.17 (1.08–1.27)	1.54 (1.31–1.82)	3.31 (2.06–5.30)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.12 (1.03–1.21)	1.23 (1.03–1.46)	2.87 (1.77–4.65)	$P<0.0003$
Hemorrhagic stroke:					
No. of strokes	451	528	33	3	
Crude	1.00	7.41 (6.54–8.40)	18.4 (12.9–26.2)	23.5 (7.57–72.9)	$P<0.0001$
Adjustment for age	1.00	1.39 (1.16–1.67)	1.86 (1.25–2.77)	3.64 (1.15–11.5)	$P<0.0001$
Multivariable adjustment[a]	1.00	1.38 (1.14–1.66)	1.70 (1.13–2.57)	3.46 (1.09–10.9)	$P<0.0001$

GFR = glomerular filtration rate.

[a]Multivariable adjustment was made for age, gender, diabetes mellitus, total cholesterol, and triglycerides.

mild renal dysfunction with decreasing GFR-Mayo, and among women the risk of stroke was in the order of 3-fold for those with GFR between 15 and 30 mL/min per 1.73 m^2. The number of events among subjects with severe renal dysfunction was small, and these observations should be interpreted cautiously.

Several formulas to estimate kidney function have been developed. We used primarily the Mayo formula since it was developed in a cohort consisting of both healthy potential kidney donors and patients with established CKD to improve classification among individuals with normal or near-normal renal function and may lead to better classification of renal function among healthy individuals (20). The more commonly used formula to estimate GFR, the MDRD study equation, was developed in a population consisting of patients with established CKD. This may lead to misclassification of renal function especially among individuals with normal or near-normal renal function.

In a previous study we used both formulas to investigate the association between decreased GFR and incidence of myocardial infarction or mortality (8). We found the associations with mortality and myocardial infarction to be stronger when GFR was estimated using the Mayo formula rather than the MDRD study equation. Similarly, in the present study we found that already mild renal dysfunction increases the risk of ischemic stroke when we use GFR-Mayo to classify renal function. The associations were weaker and only significant for moderate or severe renal dysfunction using GFR-MDRD.

We could not calibrate our creatinine assays to an international standard, which has been recommended (27). This may have been of greater disadvantage for the MDRD study equation than for the Mayo formula. Serum creatinine was measured only once in most individuals, leading to inability to adjust for intraindividual variation in values.

Table IV. Adjusted hazard ratios for stroke in different age groups in relation to GFR estimated by the Mayo formula.[a]

	GFR (mL/min/1.73 m^2)			
All subjects ($n = 539,287$)	>90 HR	60–90 GFR-Mayo HR (95% CI)	30–60 GFR-Mayo HR (95% CI)	15–30 GFR-Mayo HR (95% CI)
All stroke:				
(All ages)	1.0	1.09 (1.05–1.14)	1.43 (1.30–1.57)	2.23 (1.65–2.96)
30–65 yo ($n = 11,138$)	1.0	1.08 (1.02–1.14)	1.92 (1.52–2.41)	4.53 (2.81–7.29)
>65 yo ($n = 6,067$)	1.0	1.14 (1.06–1.22)	1.61 (1.43–1.81)	1.96 (1.34–2.83)
Ischemic stroke:				
(All ages)	1.0	1.09 (1.04–1.14)	1.24 (1.10–1.39)	2.27 (1.63–3.17)
30–65 yo ($n = 7,954$)	1.0	1.08 (1.02–1.15)	1.82 (1.39–2.38)	4.69 (2.72–8.09)
>65 yo ($n = 4,517$)	1.0	1.17 (1.08–1.27)	1.53 (1.33–1.76)	2.19 (1.43–3.36)
Hemorrhagic stroke:				
(All ages)	1.0	1.04 (0.93–1.15)	1.26 (0.96–1.64)	2.31 (1.10–4.87)
30–65 yo ($n = 1,840$)	1.0	0.99 (0.86–1.13)	2.63 (1.60–4.31)	4.49 (1.45–13.9)
>65 yo ($n = 793$)	1.0	1.13 (0.94–1.38)	1.41 (1.00–1.99)	2.17 (0.80–5.90)

CI = confidence intervals; HR = hazard ratios; GFR = glomerular filtration rate; yo = years old.
[a]Hazard ratios are presented with 95% confidence intervals after multivariable adjustment for age, gender, diabetes, total cholesterol, and triglycerides.

The main strengths of our study are the comparatively large study population, which was representative for the population of Stockholm in the 1990s, and the relatively long follow-up. The large number of stroke cases enabled us to subtype stroke and also to make gender- and age-specific analyses. In addition few patients were lost to follow-up since the Swedish population and health registers that we used are essentially complete.

Study limitations

The most important limitation of the present study is that we were not able to adjust for established risk factors for stroke, in particular blood pressure and smoking. We also lacked information on cardiovascular medication. In 8,360 women with information on smoking, no association between smoking and renal dysfunction was found, a finding consistent with other studies (6,28). In previous studies investigating the relation between CKD and cardiovascular disease, adjustment for cardiovascular risk factors other than age and gender has only changed hazard ratios marginally (6,29). In the Rotterdam study where information on cardiovascular medication, carotid intima–media thickness, serum C-reactive protein, and left ventricular hypertrophy was available and adjusted for, beside traditional cardiovascular risk factors, hazard ratios for stroke changed in general less than 0.1 compared with only adjusting for age and gender (10). Thus, it is unlikely that the associations seen would change markedly even if we could control for confounders not known to us. However, in view of possible residual confounding, our findings on the association between in particular mildly decreased GFR and first stroke should be interpreted with caution.

There are studies suggesting that the sensitivity of the stroke diagnosis was relatively low in the Nordic countries during the study period (25,26). However, a low sensitivity that is not related to level of renal function (non-differential misclassification) would most likely not substantially bias the relative risk estimates. A low specificity of stroke diagnoses that is non-differential would tend to dilute actual associations between renal dysfunction and stroke.

Conclusions

In conclusion, we found that already mild renal dysfunction is associated with an increased incidence of first stroke in a mainly healthy cohort of adults. Both ischemic stroke and hemorrhagic stroke were related to renal dysfunction. The relationship between hemorrhagic stroke and CKD was stronger among women compared with men. Similar associations were found for ischemic stroke for both genders.

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Appendix 1. Hazard ratios of stroke with 95% confidence intervals in relation to glomerular filtration rate estimated by the Modification of Diet in Renal Disease study equation.

	GFR-MDRD (mL/min/1.73 m^2)				
	>90	60–90	30–60	15–30	*P* values
Number of subjects	203,524	316,732	18,684	347	
All stroke:					
No. of strokes	3,356	12,026	2,244	52	
Crude	1.00	2.17 (2.09–2.25)	8.20 (7.77–8.65)	20.2 (15.4–26.5)	$P<0.0001$
Adjusted for age and sex	1.00	0.96 (0.92–1.00)	1.22 (1.14–1.29)	2.40 (1.82–3.16)	$P<0.0001$
Multivariable adjustment[a]	1.00	0.94 (0.91–0.98)	1.12 (1.05–1.19)	1.86 (1.40–2.46)	$P=0.0039$
Ischemic stroke:					
No. of strokes	2,284	8,886	1,646	40	
Crude	1.00	2.35 (2.24–9.36)	8.79 (8.25–9.36)	23.2 (16.6–31.7)	$P<0.0001$
Adjusted for age and sex	1.00	1.02 (0.98–1.07)	1.24 (1.15–1.33)	2.60 (1.90–3.56)	$P<0.0001$
Multivariable adjustment[a]	1.00	0.99 (0.94–1.04)	1.11 (1.03–1.20)	1.92 (1.39–2.64)	$P=0.0038$
Hemorrhagic stroke:					
No. of strokes	604	1,811	273	8	
Crude	1.00	1.80 (1.64–1.97)	5.38 (4.66–6.21)	16.4 (8.16–32.9)	$P<0.0001$
Adjusted for age and sex	1.00	0.88 (0.80–0.97)	1.00 (0.85–1.18)	2.46 (1.22–4.96)	$P=0.57$
Multivariable adjustment[a]	1.00	0.88 (0.79–0.97)	0.98 (0.83–1.16)	2.20 (1.09–4.45)	$P=0.46$

GFR = estimated glomerular filtration rate.

[a]Multivariable adjustment was made for age, gender, diabetes mellitus, total cholesterol, and triglycerides. *P* values represent test for trend.

Appendix 2. Gender-specific hazard ratios of stroke with 95% confidence intervals in relation to glomerular filtration rate estimated by the Modification of Diet in Renal Disease study equation.[a]

	eGFR (mL/min/1.73 m^2)				
	>90	60–90	30–60	15–30	*P* value
Men					
All strokes:					
No. of strokes	2,633	6,831	642	19	
Crude	1.0	2.32 (2.23–2.44)	11.3 (10.3–12.3)	12.2 (7.81–19.1)	$P<0.0001$
Adjustment for age	1.00	0.97 (0.93–1.02)	1.36 (1.23–1.49)	1.78 (1.13–2.79)	$P=0.0020$
Multivariable adjustment	1.00	0.95 (0.91–1.00)	1.24 (1.13–1.37)	1.73 (1.10–2.73)	$P=0.14$
Ischemic stroke:					
No. of strokes	1,825	5,165	485	16	
Crude	1.0	2.54 (2.40–2.67)	12.2 (11.0–13.5)	14.9 (9.13–24.4)	$P<0.0001$
Adjustment for age	1.0	1.03 (0.97–1.08)	1.36 (1.22–1.52)	2.07 (1.26–3.39)	$P<0.0001$
Multivariable adjustment	1.0	0.99 (0.94–1.05)	1.22 (1.09–1.37)	2.02 (1.23–3.32)	$P=0.023$
Hemorrhagic stroke:					
No. of strokes	493	1,095	90	3	
Crude	1.0	1.97 (1.77–2.19)	8.10 (6.47–10.14)	9.96 (3.20–31.0)	$P<0.0001$
Adjustment for age	1.00	0.87 (0.78–0.97)	1.15 (0.91–1.47)	1.79 (0.57–5.58)	$P=0.38$
Multivariable adjustment	1.00	0.88 (0.78–0.98)	1.12 (0.87–1.43)	1.78 (0.57–5.56)	$P=0.35$
Women					
All strokes:					
No. of strokes	723	5,195	1,602	33	
Crude	1.0	2.54 (2.35–2.74)	10.4 (9.5–11.4)	39.3 (27.7–55.7)	$P<0.0001$
Adjustment for age	1.00	0.93 (0.86–1.00)	1.12 (1.02–1.24)	2.92 (2.06–4.16)	$P<0.0001$
Multivariable adjustment	1.00	0.90 (0.83–0.98)	1.02 (0.93–1.13)	1.82 (1.26–2.63)	$P=0.019$
Ischemic stroke:					
No. of strokes	459	3,721	1,161	24	
Crude	1.00	2.84 (2.58–3.13)	11.8 (10.6–13.1)	46.4 (30.8–69.9)	$P<0.0001$
Adjustment for age	1.00	0.98 (0.89–1.09)	1.15 (1.02–1.29)	3.06 (2.02–4.64)	$P<0.0001$
Multivariable adjustment	1.00	0.95 (0.86–1.05)	1.01 (0.90–1.14)	1.70 (1.10–2.63)	$P=0.17$
Hemorrhagic stroke:					
No. of strokes	111	716	183	5	
Crude	1.00	2.28 (1.87–2.79)	7.60 (6.00–9.62)	35.6 (14.5–87.2)	$P<0.0001$
Adjustment for age	1.00	0.89 (0.73–1.10)	0.94 (0.73–1.22)	3.16 (1.28–7.82)	$P=0.81$
Multivariable adjustment	1.00	0.87 (0.71–1.07)	0.92 (0.71–1.20)	2.79 (1.12–6.96)	$P=0.93$

eGFR = estimated glomerular filtration rate.

[a]Multivariable adjustment was made for age, gender, diabetes mellitus, total cholesterol, and triglycerides. *P* values represent test for trend.