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Original Article

ORIGINAL ARTICLE

Incidence of and risk factors for chronic kidney disease: results of a nationwide study in Iceland

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ABSTRACT

Background. Information on the incidence of chronic kidney disease (CKD) in the general population is scarce. This study examined the incidence and risk factors of CKD stages 1–5 in Iceland, based on multiple markers of kidney damage.
Methods. All serum creatinine (SCr) values, urine protein measurements and diagnosis codes for kidney diseases and comorbid conditions for people aged ≥18 years were obtained from electronic medical records of all healthcare institutions in Iceland in 2008–2016. CKD was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as evidence for kidney damage and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for >3 months. Alternatively, CKD was defined using age-adapted eGFR thresholds. Mean annual age-standardized incidence of CKD was calculated for persons without CKD at study entry. Risk factor assessment was based on International Classification of Diseases diagnosis codes. Incidence was reported per 100 000 population.
Results. We retrieved 1 820 990 SCr values for 206 727 persons. Median age was 45 years (range, 18–106) and 47% were men. Mean annual age-standardized incidence of CKD per 100 000 was 649 in men and 694 in women, and 480 in men and 522 in women using age-adapted eGFR thresholds. The incidence reached over 3000 in men and women aged >75 years. Traditional CKD risk factors, such as acute kidney injury, diabetes, hypertension and cardiovascular disease, as well as less well characterized risk factors, including chronic lung disease, malignancy and major psychiatric illness were associated with increased risk of CKD, and the same was true for obesity and sleep apnoea in women.
Conclusion. The annual incidence of CKD, with strict adherence to the KDIGO criteria, was <0.7% but markedly lower using age-adapted eGFR thresholds. Apart from acute kidney injury, the observed risk factors comprised chronic and potentially modifiable disorders.

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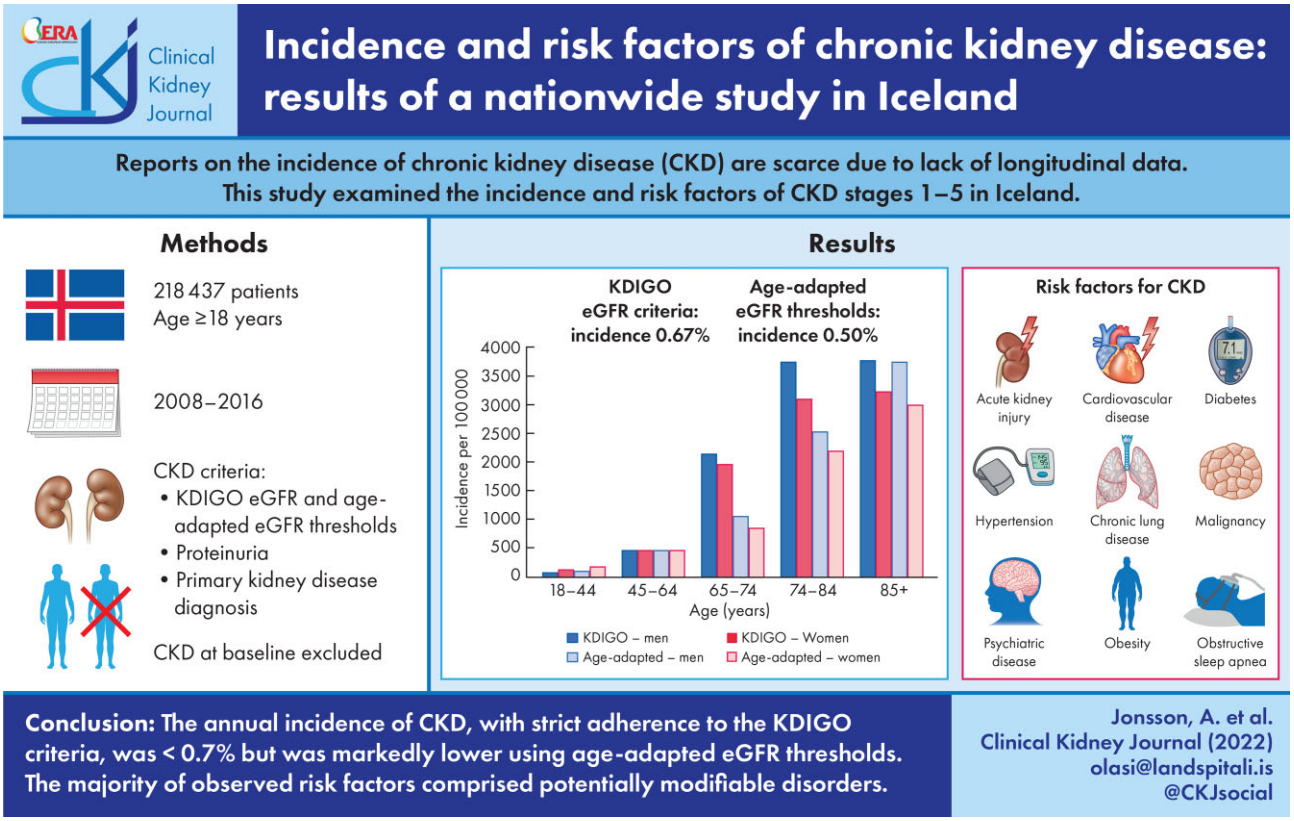
GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, eGFR, incidence, KDIGO criteria, risk factors

INTRODUCTION

Numerous studies on the prevalence of chronic kidney disease (CKD) in diverse populations have been reported [1]. Assessing the incidence of CKD is more cumbersome as it requires longitudinal data for identification of new cases.

In the past, most studies on incidence of CKD have focused on end-stage kidney disease (ESKD), defined as the receipt of renal replacement therapy (RRT), as it is registered in most countries and information therefore readily available [2, 3]. Recent studies have shown that the crude incidence of ESKD has increased in both the USA and Europe over the past decades, and although the age-standardized incidence has declined or levelled off in recent years [4, 5], the global burden of ESKD is likely to increase in the next decade [2].

Only few studies exploring the incidence of earlier stages of CKD in the general population have been reported, demonstrating incidence rates ranging from 76.7 to 479 per 100 000 [6–8]. An important limitation of these studies is incomplete definition of CKD in addition to ignoring markers of kidney damage other than proteinuria [6, 7]. Studies identifying incident CKD stringently based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition, including the required 90-day duration for both estimated glomerular filtration rate (eGFR) and proteinuria, are lacking and the same applies to the use of other markers of kidney damage. Using multiple factors in the definition of kidney damage will likely more accurately estimate the true incidence of CKD [9, 10].

Commonly reported risk factors for CKD include diabetes, hypertension, vascular disease and history of acute kidney injury (AKI) [11–13]. However, studies examining the association between risk factors and incident CKD, robustly defined according to the KDIGO criteria in the general population, have not been published [9].

The purpose of this study was to estimate the incidence rate of CKD stages 1–5 based on the KDIGO definition or age-adapted eGFR thresholds in the Icelandic population and to assess possible risk factors for CKD development.

MATERIALS AND METHODS

Ethical approval

The study was approved by the National Bioethics Committee of Iceland (VSN 13–138).

Study design and data collection

The study population has previously been described in detail [14]. Briefly, data were collected retrospectively and included all inhabitants of Iceland aged 18 years or older who had one or more serum creatinine (SCr) measurements available in the years 2008–2016. We obtained all SCr values and urine protein and albumin determinations. We also retrieved all available glycated haemoglobin (HbA1c) values. Data on age, sex, hospital discharges and diagnoses of kidney disease and comorbid

conditions based on International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes were obtained from the nationwide electronic medical record system, as well as the date of death. Study entry for each individual was defined as the date of his/her first SCr measurement.

Definition of CKD

CKD was defined according to the KDIGO clinical practice guideline [15]. At least two determinations of eGFR <60 mL/min/1.73 m^2 >90 days apart were required, preferably derived from outpatient SCr values. Measurements obtained during an episode of transient SCr elevation consistent with AKI, as defined by the KDIGO criteria, were excluded [16, 17]. CKD was also defined by the presence of persistent proteinuria manifested as urinary albumin excretion rate (AER) ≥30 mg/24 h, urinary protein excretion rate (PER) ≥150 mg/24 h, urine albumin-to-creatinine ratio ≥30 mg/g or urine dipstick value of 1+ or greater in at least two consecutive measurements >90 days apart, in the absence of a urinary tract infection defined as a positive dipstick test for leukocyte esterase or nitrates. Proteinuria that was not consistently present was considered non-persistent proteinuria and was not used for identification of CKD. In addition, primary kidney disease diagnosis codes were used as markers of kidney damage [14]. After identification of CKD, staging of the disorder was carried out according to eGFR using the KDIGO classification system [15].

An alternative definition of CKD was based on age-adapted eGFR thresholds of <75 mL/min/1.73 m^2 for persons aged <40 years, <60 mL/min/1.73 m^2 for those aged between 40 and 65 years and <45 mL/min/1.73 m^2 for persons aged >65 years [18].

Definition of incident CKD

Incidence of CKD was examined overall and for different stages based on eGFR (stages G1–G5). Albuminuria stages (A1–A3) were not examined separately. For incidence of CKD stages 1–5, all persons with confirmed absence of CKD at study entry were included. For definitions of incident CKD stages 1–2, 3–5, 4–5 and 5, and RRT, all persons with no evidence of the same CKD stage at study entry were included.

Definitions of comorbid conditions

We used the ICD-9 and ICD-10 diagnosis codes or biochemical markers to define comorbid conditions as previously described [14]. In addition, diabetes was categorized by levels of HbA1c and Hospital Frailty Risk Score was calculated from diagnosis codes and classified as outlined by Gilbert *et al.* [19].

Statistical analysis

Comparison of groups was performed employing Chi-squared test and ANOVA. Annual age-standardized incidence was calculated for CKD stages 1–5, 1–2, 3–5, 4–5 and 5, as well as for RRT, in relation to the population of persons aged ≥18 years in Iceland, who numbered 258 565 on 31 December 2016. Incidence was standardized to the EU 27 population. Calculation of mean annual incidence, stratified by age groups and sex, was carried out by dividing the number of cases each year by the number of individuals at risk with confidence intervals calculated according to the method described by Fay *et al.* [20]. Lifetime risk of CKD was estimated by cumulative incidence calculated according to Fine–Gray model. Persons were censored at death, accounting for death as a competing risk. Cumulative risk calculations were based on persons with available SCr measurement who were at risk for incident CKD. Risk factor analysis was based on medical conditions existing prior to the development of CKD. The earliest date of documentation of each risk factor was used in the analysis. Hazard ratios (HR) for CKD risk factors were estimated using Cox regression. Individuals entered the risk set at the age of first SCr measurement, were followed-up until the time of CKD identification and were censored at the time of death or at the end of follow-up (31 December 2016). Models were adjusted for age by using chronological age as a timescale. Risk of developing CKD stages 1–2, CKD stages 3–5 and CKD stages 4–5 was estimated in separate models. When estimating the risk of CKD stages 1–2, individuals who had progressed to CKD stages 3–5 prior to CKD stages 1–2 were censored at the time of CKD stages 3–5. Risk factors were handled in a time-dependent manner based on the date of first documented diagnosis of each condition. All statistical analyses were performed using R version 4.0.2 (www.r-project.org) in RStudio.

RESULTS

Characteristics of the cohort

We obtained a total of 2 120 147 SCr measurements from 218 437 inhabitants in Iceland, aged ≥18 years in 2008–2016. Figure 1 demonstrates the derivation of the cohorts used for incidence calculations. The number of persons at risk for developing different stages of CKD varied. After excluding 11 710 persons who were identified with CKD upon study entry, 206 727 with SCr measurements remained at risk for developing CKD, of whom 109 023 (52.7%) were women. These persons had 1 820 990 SCr measurements available, with a median of 4 [interquartile range (IQR), 2–10] per person. A total of 237 392 urine protein measurements were available for 75 811 of these persons, with a median of 2 (IQR, 1–3) values per person.

Incidence of CKD

Of the 206 727 persons at risk, a total of 14 286 (6.9%) developed incident CKD stages 1–5 during the study period. Tables 1 and 2 show the characteristics of persons who developed CKD compared with those who did not. The average time from study entry to CKD identification was 3.4 years (IQR, 1.3–5.2) and varied somewhat for the different stages of CKD (Supplementary data, Table S1). Individuals who developed CKD were older, with a higher prevalence of comorbid conditions. The majority were found to have CKD stage 3A as the initial stage. The mean annual age-standardized incidence of CKD per 100 000 population was 671 [95% confidence interval (95% CI) 657–685] for the entire group, 649 (95% CI 630–668) for men and 694 (95% CI 674–714) for women (Table 3). The incidence increased markedly in the age groups ≥65 years, reaching approximately 4000 in men and 3000 in women per 100 000 (Figure 2). The same trend in incidence with advancing age was seen for all stages of CKD (Figure 2). Using the age-adapted eGFR thresholds, the overall incidence per 100 000 was 501 (95% CI 490–513) and was higher for women than men (Table 3). The lifetime risk of CKD stages 1–5 presented as cumulative incidence is displayed in Figure 3 and stratified by age and sex in Supplementary data, Table S2. Approximately 30% of persons with prevalent CKD had received a CKD diagnosis (N18 or N19), compared with only 11.5% of those with incident CKD. Men were more likely

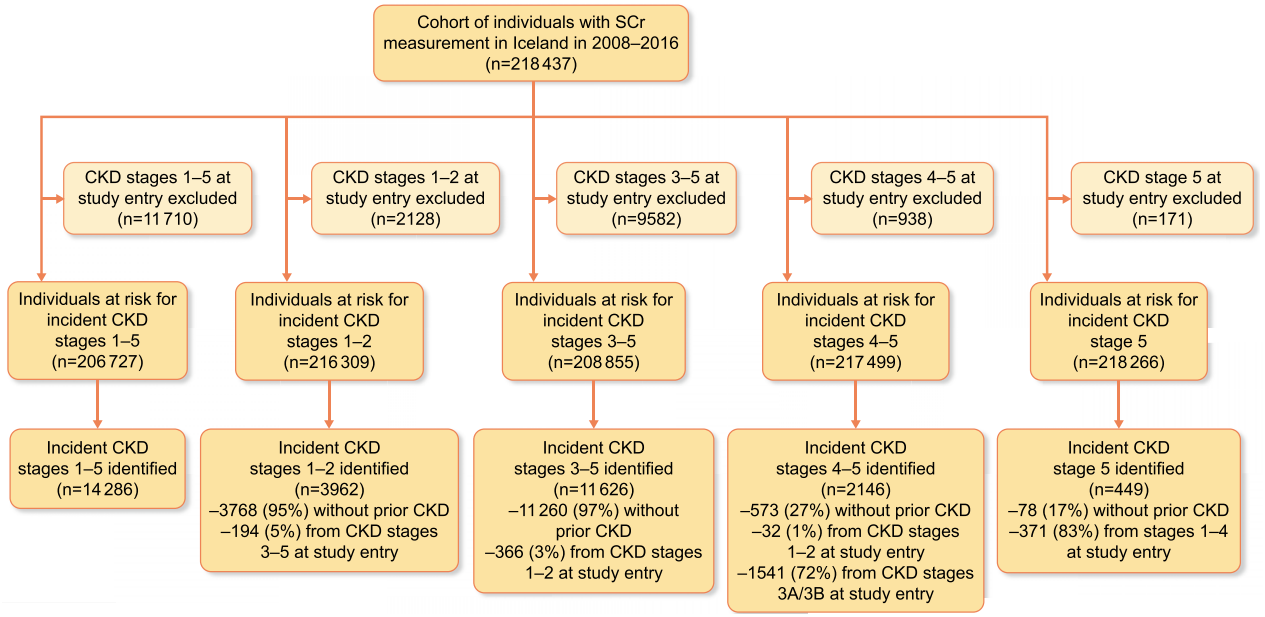


FIGURE 1: Flowchart demonstrating derivation of cohorts used for defining incident CKD, both overall and different stages. CKD, chronic kidney disease.

Table 1. Characteristics of persons with and without incident CKD during the study period

	No CKD (*N* = 192 441)	CKD stages 1–5 (*N* = 14 286)
Age at study entry, years	44 (18–106)	69 (18–106)
Sex, women	101 705(52.8)	7318 (52.2)
Mean time to CKD, years (IQR)	–	3.4 (1.3–5.2)
First CKD stage observed[a]		
Stage 1	–	1762 (12.3)
Stage 2	–	1811 (12.7)
Stage 3A	–	9676 (67.7)
Stage 3B	–	952 (6.7)
Stage 4	–	68 (0.5)
Stage 5	–	17 (0.1)
Persistent proteinuria[b]		
At first CKD identification	–	2850 (19.9)
In the study period	–	3147 (22.0)
CKD based on kidney-specific diagnosis[c]		
Diagnosis		
At first CKD identification	–	1717 (12.0)
In the study period	–	2423 (17.0)

Data presented as number (%) or mean (range).
[a]CKD stages 1–2 were identified based on kidney damage evident by either persistent proteinuria or primary kidney disease diagnosis.
[b]Defined as urinary AER ≥30 mg/24 h, urinary PER ≥150 mg/24 h, urine albumin-to-creatinine ratio ≥30 mg/g or urine dipstick value of 1+ or greater in at least two consecutive measurements >90 days apart, in the absence of a urinary tract infection defined as a positive dipstick test for leukocyte esterase or nitrates.
[c]Kidney-specific diagnosis defined as primary kidney disease diagnosis, incorporated for evidence of kidney damage.
IQR, interquartile range; CKD, chronic kidney disease; AER, urinary albumin excretion rate; PER, urinary protein excretion rate.

to receive a CKD diagnosis than women (Supplementary data, Table S3).

Incidence of different CKD stages

The mean annual age-standardized incidence of different stages of CKD is displayed in Table 3. The mean annual age-standardized incidence of CKD stages 1–2 was 178 (95% CI 172–186) per 100 000 and was higher in men. For CKD stages 3–5, the incidence was 547 (95% CI 535–560) per 100 000 and was higher in women. Using the age-adapted eGFR thresholds, the incidence of CKD stages 3–5 was somewhat lower or 328 (95% CI 318–337) per 100 000. For CKD stages 1–2 and CKD stages 3–5, 95% and 97% of persons, respectively, were previously identified as not having evidence for CKD (Figure 1). For CKD stages 4–5, the mean annual age-standardized incidence per 100 000 was 91 (95% CI 86–96) and was higher in women. The age-standardized incidence of CKD stage 5 was 19 (95% CI 17–22) per 100 000, with no difference between men and women. For CKD stages 4–5 and CKD stage 5, the vast majority of individuals progressed from earlier CKD stages (Figure 1). A total of 229 individuals initiated RRT during the study period, yielding a mean annual age-standardized incidence of 11 (95% CI 9–12) per 100 000, with no difference between men and women (Table 3).

Risk factors for CKD

Overall, there was a similar pattern of risk factor association with CKD development for both men and women. For incident CKD stages 1–2, the multivariate model identified diabetes, AKI, kidney stones, hypertension, cerebrovascular disease, malignancy and increased frailty as significant risk factors for both men and women. Of these, diabetes showed the strongest association in the multivariable model, especially when defined as HbA1c >8% (Table 4). For CKD stages 3–5, AKI showed a particularly strong association in both men and women, followed

Table 2. Comorbid conditions of the study cohort, mostly based on ICD-9 and ICD-10 diagnosis codes

	No CKD (N = 192 441)	Incident CKD stages 1–5 (N = 14 286)	P-value
Hypertension	48 255 (25.1)	9770 (68.4)	<0.001
Diabetes mellitus—ICD[a]	9220 (4.8)	3573 (25.0)	<0.001
Diabetes mellitus—ICD + HbA1c[b]	20 840 (10.8)	5445 (38.1)	<0.001
Coronary artery disease	14 832 (7.7)	5137 (36.0)	<0.001
Congestive heart failure	4113 (2.1)	2846 (19.9)	<0.001
Atrial fibrillation/flutter	7826 (4.1)	3334 (23.3)	<0.001
Cerebrovascular disease	5990 (3.1)	2026 (14.2)	<0.001
Peripheral vascular disease	6616 (3.4)	1841 (12.9)	<0.001
Hyperlipidemia	22 807 (11.9)	4429 (31.0)	<0.001
Obesity	18 837 (9.8)	2043 (14.3)	<0.001
Chronic lung disease	35 236 (18.3)	4379 (30.7)	<0.001
Obstructive sleep apnoea	9247 (4.8)	1554 (10.9)	<0.001
Kidney stones	7408 (3.8)	1193 (8.4)	<0.001
Malignancy	32 211 (16.7)	4516 (31.6)	<0.001
Substance abuse	25 213 (13.1)	1829 (12.8)	0.31
Psychiatric disease	42 213 (21.9)	3805 (26.6)	<0.001
Acute kidney injury[c]	11 064 (5.7)	4887 (34.2)	<0.001
AKI stage 1[e]	9261 (83.7)	3730 (76.3)	<0.001
AKI stage 2[e]	1333 (12.1)	842 (17.2)	<0.001
AKI stage 3[e]	470 (4.2)	315 (6.5)	<0.001
Frailty risk score[d]			
Low	106 591 (55.4)	3030 (21.2)	<0.001
Intermediate	75 825 (39.4)	7060 (49.4)	<0.001
High	10 025 (5.2)	4196 (29.4)	<0.001

The data represent prevalent conditions in the study period. Data are presented as number (%).
[a]Diabetes defined by registered ICD codes.
[b]Diabetes defined by registered ICD codes or HbA1c ≥6.5%.
[c]Acute kidney injury episodes were determined according to the serum creatinine component of the KDIGO criteria.
[d]Frailty Risk Score categorization: low risk: <5; intermediate risk: 5–15; high risk: >15.
[e]Only attributable to individuals identified as having AKI.
AKI, acute kidney injury; CKD, chronic kidney disease.

Table 3. Age-standardized mean annual incidence of different stages of CKD

	Incidence per 100 000 per year (95% CI)		
Stages of CKD	All	Men	Women
CKD stages 1–5	671 (657–685)	649 (630–668)	694 (674–714)
CKD stages 1–5[a]	501 (490–513)	480 (464–497)	522 (505–540)
CKD stages 1–2	178 (172–186)	198 (188–209)	159 (150–169)
CKD stages 3–5	547 (535–560)	515 (498–533)	579 (561–597)
CKD stages 3–5[a]	328 (318–337)	286 (274–299)	369 (355–384)
CKD stages 4–5	91 (86–96)	82 (75–89)	99 (92–107)
CKD stages 5	19 (17–22)	20 (17–24)	18 (15–21)
RRT	11 (9–12)	13 (10–16)	8 (6–11)

[a]CKD based on age-adapted eGFR thresholds.
CKD, chronic kidney disease; RRT, renal replacement therapy.

by hypertension and various cardiovascular diseases, whereas a weaker but significant association was observed for diabetes with the greatest effect size for HbA1c >8% (Table 5). While persistent proteinuria was included in the definition of CKD, any proteinuria was also evaluated as a risk factor developing CKD stages 3–5, revealing a statistically significant association. Obesity and obstructive sleep apnoea showed a significant association in women. History of malignancy, major psychiatric disorders and chronic lung disease also associated with incident CKD stages 3–5. For development of CKD stages 4–5, women were found to have a greater number of significant risk factors than men (Table 6). AKI had the strongest association for both men and women. Furthermore, hypertension, cardiovascular diseases and all categories of diabetes associated with incident CKD stages 4–5. Increased frailty score associated with decreased risk of development of CKD stages 3–5 and 4–5 (Tables 5 and 6).

DISCUSSION

In this nationwide study that included the majority of the Icelandic population aged 18 years or older, the overall age-standardized incidence of CKD was approximately 0.7% when a stringent definition based on the KDIGO criteria was used. The incidence increased with advancing age for all stages of CKD. However, applying age-adapted eGFR thresholds for identification of CKD results in a markedly lower incidence. Cumulative incidence was noted to be higher in women at younger age and higher in older men. Risk factors for the development of CKD showed a similar pattern for men and women, with AKI, hypertension, diabetes and cardiovascular disease being most significant.

Few studies have been reported on the incidence of CKD in the general population. The community-based EPidémiologie de l'Insuffisance Rénale chronique dans l'Agglomération Nancéienne (EPIRAN) study estimated the incidence of CKD in a population in Eastern France [7]. The authors identified persons with persistently elevated SCr and defined CKD as eGFR <60 mL/min/1.73 m^2, calculated using the modification of diet in renal disease equation. The overall age-standardized

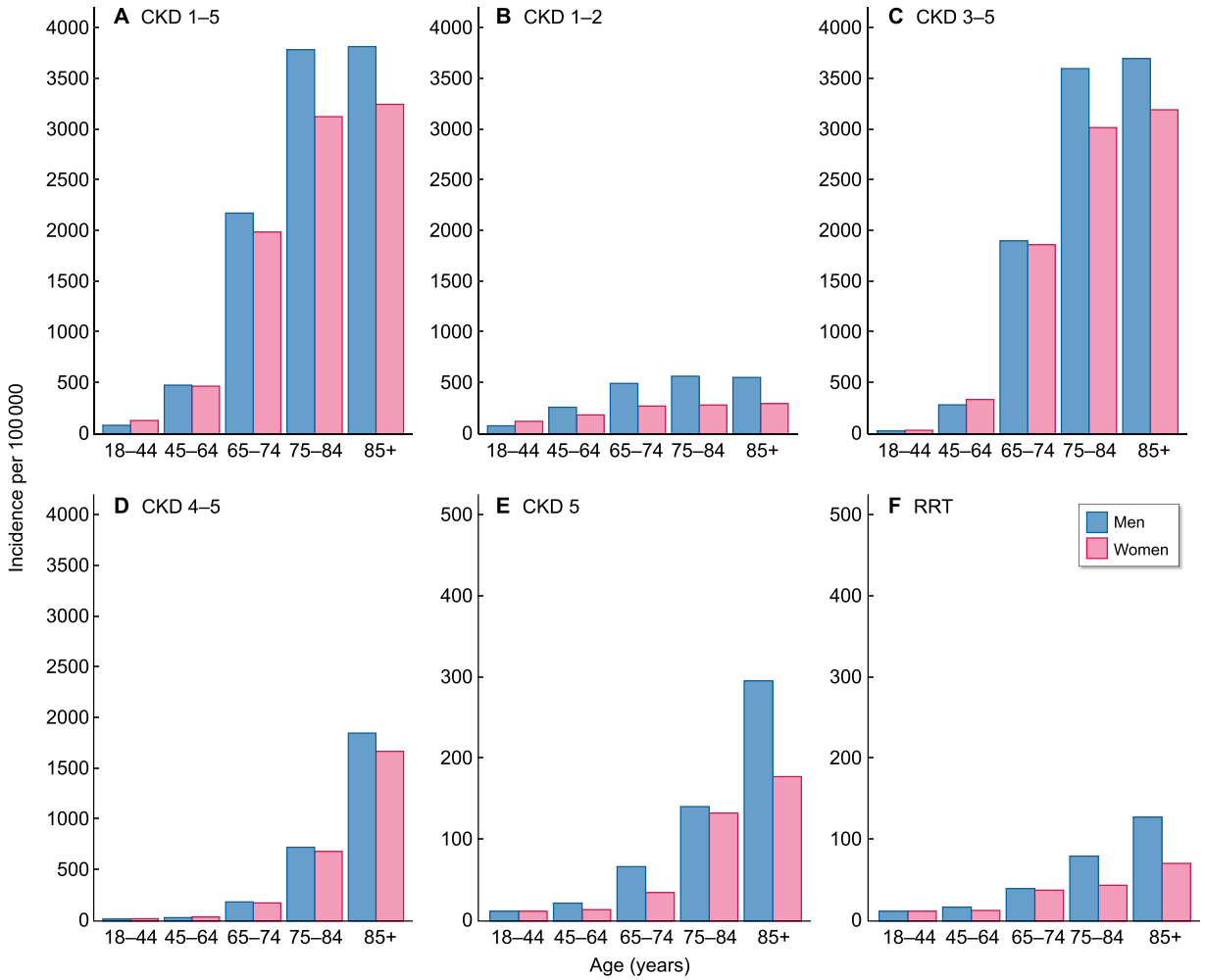


FIGURE 2: (**A–F**) Age-standardized mean annual incidence of different CKD stages according to age groups and sex. (**A**) CKD stages 1–5. (**B**) CKD stages 1–2. (**C**) CKD stages 3–5. (**D**) CKD stages 4–5. (**E**) CKD stage 5. (**F**) Renal replacement therapy. Note difference range on y-axis in panels E and F.

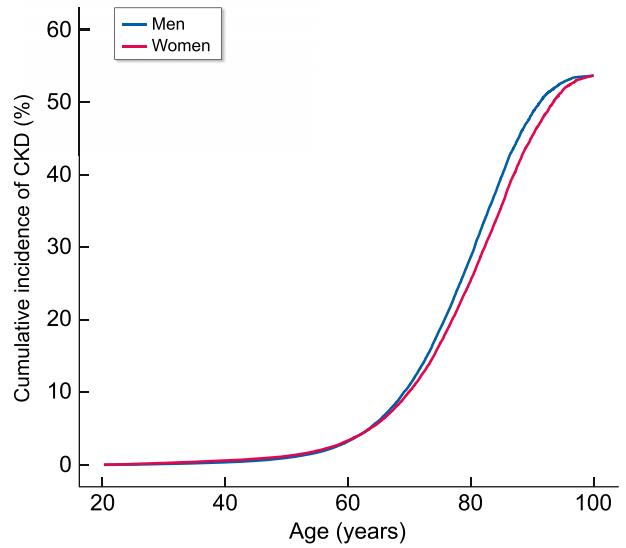


FIGURE 3: Cumulative incidence (lifetime risk) of CKD stages 1–5 for men and women. CKD, chronic kidney disease.

incidence was 767.1 per million population (pmp), which is approximately 7 times lower than in our study. The methods used for identification of CKD differed from ours as we used persistent proteinuria and a kidney-specific diagnosis as markers of kidney damage, in addition to reduced eGFR. Furthermore, a single creatinine cut-off value of ≥1.7 mg/dL for identification of individuals at risk of CKD was used in the EPIRAN study, which is likely to result in underestimation of the CKD incidence. The same notion applies when comparison is made with a study by Drey *et al.* [6] in a general cohort in the UK. The investigators observed an incidence of 1701 pmp when elevated SCr was used for definition of CKD. Another study by van Blijderveen *et al.* based on data from a primary care database in the Netherlands, using both eGFR and proteinuria to define CKD, showed an age-standardized incidence of 479 per 100 000 person-years when the 90-day criterion was included, compared with 1213 per 100 000 person-years when this criterion was not required [8]. These findings are more consistent with the results of our study, although we included data from hospitals and outpatient specialty care and used kidney disease diagnoses to define CKD, in addition to eGFR and proteinuria. Although the use of diagnosis codes lacks sensitivity and therefore is likely to underreport the incidence of CKD, their addition to other criteria nevertheless would be expected to better reflect the true incidence of CKD [8].

Table 4. Association between risk factors and incident CKD stages 1–2 for women and men

	Men				Women			
	Univariate		Multivariate		Univariate		Multivariate	
Risk factors	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI
Hypertension	2.09	1.90–2.31	**1.35**	**1.22–1.50**	1.99	1.77–2.24	**1.30**	**1.14–1.47**
Diabetes mellitus								
– HbA1c <6.5%[a]	4.38	3.39–5.66	**3.63**	**2.80–4.71**	4.40	3.29–5.89	**3.58**	**2.66–4.81**
– HbA1c 6.5%–8.0%[a]	4.64	4.06–5.30	**4.05**	**3.53–4.65**	3.68	3.10–4.35	**3.18**	**2.67–3.78**
– HbA1c >8.0%[a]	10.62	9.55–11.80	**8.96**	**8.01–10.03**	13.85	12.16–15.76	**11.31**	**9.84–13.00**
Coronary artery disease	1.46	1.31–1.64	0.90	0.79–1.01	1.71	1.44–2.04	1.03	0.86–1.24
Congestive heart failure	2.12	1.76–2.54	1.13	0.93–1.38	2.35	1.80–3.06	1.25	0.95–1.66
Atrial fibrillation/flutter	1.56	1.34–1.81	1.12	0.95–1.31	1.32	1.02–1.70	0.83	0.63–1.08
Cerebrovascular disease	1.77	1.50–2.09	**1.31**	**1.11–1.56**	1.76	1.39–2.22	**1.33**	**1.05–1.68**
Peripheral vascular disease	1.42	1.20–1.69	1.09	0.91–1.29	1.70	1.37–2.11	**1.38**	**1.11–1.71**
Hyperlipidemia	1.34	1.21–1.50	0.95	0.85–1.06	1.49	1.29–1.72	1.01	0.88–1.17
Obesity	2.19	1.93–2.49	1.01	0.88–1.16	1.94	1.72–2.20	1.09	0.96–1.25
Chronic lung disease	1.29	1.15–1.45	1.03	0.91–1.16	1.36	1.22–1.52	1.07	0.95–1.21
Obstructive sleep apnoea	1.76	1.53–2.02	1.02	0.88–1.18	1.94	1.53–2.47	0.97	0.75–1.24
Kidney stones	1.62	1.32–2.00	**1.59**	**1.29–1.96**	2.67	2.11–3.43	**2.70**	**2.11–3.46**
Malignancy	1.82	1.61–2.06	**1.63**	**1.44–1.84**	1.22	1.08–1.39	**1.13**	**1.00–1.28**
Psychiatric disease	0.97	0.83–1.13	0.93	0.79–1.10	1.08	0.94–1.23	1.04	0.90–1.20
Acute kidney injury	2.93	2.56–3.36	**1.68**	**1.46–1.93**	2.49	2.13–2.91	**1.52**	**1.29–1.78**
Intermediate frailty risk score	1.97	1.79–2.17	**1.41**	**1.27–1.56**	1.66	1.50–1.85	**1.25**	**1.11–1.40**
Severe frailty risk score	2.01	1.68–2.41	**1.22**	**1.01–1.47**	2.25	1.89–2.68	**1.36**	**1.12–1.64**

Cox proportional hazards model.
[a]Diabetes mellitus identified by ICD diagnosis codes or HbA1c (% or mmol/mol) and stratified by worst HbA1c measurement in the study period.
Statistically significant risk factors in the multivariate model are highlighted in bold.
CKD, chronic kidney disease.

Table 5. Association between risk factors and incident CKD stages 3–5 for women and men

	Men				Women			
	Univariate		Multivariate		Univariate		Multivariate	
Risk factors	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI
Hypertension	1.75	1.66–1.86	**1.62**	**1.53–1.72**	1.83	1.73–1.93	**1.74**	**1.64–1.85**
Diabetes mellitus								
– HbA1c <6.5%[a]	1.53	1.29–1.80	**1.26**	**1.06–1.48**	1.69	1.43–1.99	**1.28**	**1.09–1.52**
– HbA1c 6.5%–8.0%[a]	1.41	1.30–1.54	1.05	0.97–1.15	1.46	1.34–1.60	1.09	0.99–1.19
– HbA1c >8.0%/64[a]	1.64	1.50–1.79	**1.17**	**1.07–1.28**	1.71	1.54–1.91	**1.22**	**1.09–1.36**
Proteinuria[b]	2.08	1.94–2.23	**1.45**	**1.34–1.56**	1.74	1.60–1.89	**1.26**	**1.15–1.38**
Coronary artery disease	1.65	1.56–1.75	**1.37**	**1.29–1.46**	1.77	1.67–1.88	**1.48**	**1.39–1.58**
Congestive heart failure	2.74	2.54–2.95	**1.93**	**1.77–2.10**	2.46	2.27–2.68	**1.57**	**1.43–1.72**
Atrial fibrillation/flutter	1.57	1.46–1.68	**1.12**	**1.04–1.21**	1.92	1.78–2.07	**1.46**	**1.35–1.58**
Cerebrovascular disease	1.34	1.23–1.45	**1.32**	**1.21–1.44**	1.30	1.19–1.42	**1.22**	**1.11–1.34**
Peripheral vascular disease	1.46	1.35–1.58	**1.26**	**1.16–1.37**	1.47	1.34–1.61	**1.27**	**1.16–1.40**
Hyperlipidemia	1.13	1.06–1.20	0.95	0.89–1.01	1.16	1.09–1.23	1.00	0.94–1.06
Obesity	1.40	1.27–1.54	1.06	0.96–1.18	1.43	1.32–1.55	**1.17**	**1.07–1.27**
Chronic lung disease	1.23	1.17–1.33	**1.12**	**1.05–1.20**	1.26	1.19–1.33	**1.13**	**1.07–1.20**
Obstructive sleep apnoea	1.32	1.21–1.45	1.06	0.97–1.17	1.51	1.33–1.70	**1.21**	**1.07–1.37**
Kidney stones	0.95	0.82–1.11	1.01	0.87–1.18	1.00	0.80–1.24	1.07	0.86–1.34
Malignancy	1.52	1.42–1.62	**1.46**	**1.37–1.56**	1.35	1.27–1.43	**1.31**	**1.23–1.40**
Psychiatric disease	0.96	0.86–1.08	**1.20**	**1.06–1.35**	1.04	0.95–1.12	**1.28**	**1.17–1.39**
Acute kidney injury	3.64	3.40–3.90	**2.90**	**2.70–3.12**	3.12	2.93–3.34	**2.73**	**2.55–2.93**
Intermediate frailty risk score	0.93	0.88–0.99	**0.61**	**0.58–0.65**	1.05	0.99–1.10	**0.68**	**0.64–0.72**
Severe frailty risk score	0.52	0.46–0.57	**0.26**	**0.23–0.29**	0.64	0.59–0.70	**0.31**	**0.28–0.34**

Cox proportional hazards model.
[a]Diabetes mellitus identified by ICD diagnosis codes or HbA1c (% or mmol/mol) and stratified by worst HbA1c measurement in the study period.
[b]Persistent and non-persistent proteinuria defined as: urinary AER ≥30 mg/24 h, urinary PER ≥150 mg/24 h, urine albumin-to-creatinine ratio ≥30 mg/g or urine dipstick value of 1+ or greater, in the absence of a urinary tract infection defined as a positive dipstick test for leukocyte esterase or nitrates, with (persistent) or without (non-persistent) requirement of at least two consecutive measurements >90 days apart.
Statistically significant risk factors in the multivariate model are highlighted in bold.
CKD, chronic kidney disease; AER, urinary albumin excretion rate; PER, urinary protein excretion rate.

Table 6. Association between risk factors and incident CKD stages 4–5 for women and men

	Men				Women			
	Univariate		Multivariate		Univariate		Multivariate	
Risk factors	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI	Hazard ratio	CI
Hypertension	2.98	2.22–3.99	**2.07**	**1.52–2.82**	2.33	1.75–3.11	**1.74**	**1.64–1.85**
Diabetes mellitus								
– HbA1c <6.5%[a]	2.44	1.38–4.32	1.21	0.68–2.16	4.91	3.29–7.32	**1.28**	**1.09–1.52**
– HbA1c 6.5%–8.0%[a]	2.85	2.06–3.93	**1.67**	**1.20–2.33**	2.60	1.87–3.62	**1.09**	**0.99–1.19**
– HbA1c >8.0%[a]	3.78	2.72–5.24	**1.96**	**1.39–2.78**	4.53	3.18–6.45	**1.22**	**1.09–1.36**
Proteinuria[b]	6.64	5.19–8.50	**2.62**	**2.00–3.43**	5.87	4.61–7.46	**1.26**	**1.15–1.38**
Coronary artery disease	2.07	1.60–2.67	1.07	0.81–1.42	2.60	2.04–3.30	**1.48**	**1.39–1.58**
Congestive heart failure	6.02	4.60–7.89	**2.34**	**1.72–3.20**	6.73	5.20–8.69	**1.57**	**1.43–1.72**
Atrial fibrillation/flutter	2.38	1.82–3.12	1.05	0.78–1.40	3.27	2.53–4.24	**1.46**	**1.35–1.58**
Cerebrovascular disease	1.38	0.98–1.94	0.97	0.68–1.37	1.28	0.90–1.82	**1.22**	**1.11–1.34**
Peripheral vascular disease	2.15	1.59–2.91	**1.40**	**1.02–1.91**	1.58	1.11–2.26	**1.27**	**1.16–1.40**
Hyperlipidemia	1.19	0.90–1.56	0.87	0.65–1.16	1.25	0.97–1.61	1.00	0.94–1.06
Obesity	1.74	1.17–2.57	0.78	0.51–1.19	2.88	2.12–3.90	**1.17**	**1.07–1.27**
Chronic lung disease	1.61	1.23–2.11	1.09	0.82–1.44	1.43	1.12–1.82	**1.13**	**1.07–1.20**
Obstructive sleep apnoea	1.53	1.03–2.25	0.90	0.59–1.35	2.67	1.74–4.11	**1.21**	**1.07–1.37**
Kidney stones	1.03	0.53–2.01	0.99	0.51–1.94	0.74	0.24–2.29	1.07	0.86–1.34
Malignancy	1.60	1.22–2.10	1.23	0.93–1.62	1.25	0.96–1.63	**1.31**	**1.23–1.40**
Psychiatric disease	0.82	0.46–1.46	1.02	0.57–1.85	1.12	0.77–1.63	**1.28**	**1.17–1.39**
Acute kidney injury	15.52	12.02–20.03	**8.36**	**6.29–11.12**	12.26	9.67–15.53	**2.73**	**2.55–2.93**
Intermediate frailty risk score	1.13	0.87–1.46	**0.69**	**0.53–0.90**	1,21	0.94–1.57	**0.68**	**0.64–0.72**
Severe frailty risk score	0.58	0.36–0.93	**0.30**	**0.19–0.48**	0.62	0.42–0.90	**0.31**	**0.28–0.34**

Cox proportional hazards model.

[a]Diabetes mellitus identified by ICD diagnosis codes or HbA1c (% or mmol/mol) and stratified by worst HbA1c measurement in the study period.

[b]Persistent and non-persistent proteinuria defined: urinary AER ≥30 mg/24 h, urinary PER ≥150 mg/24 h, urine albumin-to-creatinine ratio ≥30 mg/g or urine dipstick value of 1+ or greater, in the absence of a urinary tract infection defined as a positive dipstick test for leukocyte esterase or nitrates, with (persistent) or without (non-persistent) requirement of at least two consecutive measurements >90 days apart.

Statistically significant risk factors in the multivariate model are highlighted in bold.

CKD, chronic kidney disease; AER, urinary albumin excretion rate; PER, urinary protein excretion rate.

Interestingly, only about 11% of persons who were identified with incident CKD in the current study had a documented diagnosis of CKD, suggesting underreporting and/or unawareness among physicians. Men were more likely to be assigned a CKD diagnosis than women. The reasons for this are unclear and might indicate inconsistencies in the management of CKD among physicians.

As expected, we detected a significant association between hypertension, diabetes and AKI, and the development of all stages of CKD. In addition, we found cardiovascular disease to be associated with development of CKD stages 3–5. These findings are in line with previous studies [2, 11–13, 21, 22]. For diabetes, the HR was highest for CKD stages 1–2, especially among those with HbA1c >8%. The less significant association between diabetes and development of CKD stages 3–5 might be explained by inadequate time for individuals with CKD stages 1–2 to progress to more advanced stages or a competing risk of death before the development of CKD in diabetics [23].

Obesity was associated with development of CKD stages 3–5 in women. Previous studies have demonstrated that obesity is a risk factor for CKD [13, 24] and proteinuria [25]. Although increased risk of CKD might be mediated through comorbid conditions associated with obesity [26], it is also conceivable that obesity has unique effects on kidney function [27]. In our analysis, we used ICD diagnosis codes for identification of obesity which likely underestimates its prevalence, precluding detailed assessment of the role of obesity. Moreover, we did not account for waist circumference or hyperlipidemia analysis for better understanding of the effects of factors comprising the metabolic syndrome, which may be of more importance than obesity itself [26].

CKD is known to be common among patients with malignancies, although few studies have explored the incidence of CKD in persons with a history of cancer [27]. We found malignancy to be a risk factor for development of CKD stages 3–5 in both men and women. We were neither able to determine which types of malignant disorders carry increased risk for CKD, nor was it possible to establish whether the increased risk was mediated by the cancer itself or by treatment-related mechanisms. Further studies on incident CKD after development of cancer are needed. Likewise, the association between frailty and CKD requires further study.

Chronic lung disease is a less well recognized risk factor for CKD. Although existing evidence is limited, prior studies do support our findings [28, 29]. Likewise, increased risk of CKD in patients with major psychiatric illness has not been well characterized, but may in part be related to lithium treatment [30]. While additional studies are needed to define the risk of CKD in these patient populations, our results suggest that monitoring of kidney function should be an integral part of their long-term care.

Kidney stones were a significant risk factor for development of CKD stages 1–2 for both men and women. However, for higher CKD stages, a significant association was not detected. Increased risk of CKD has been observed among individuals with kidney stones in several studies carried out in the general population [31–33], though not all [34]. Most have defined CKD solely based on reduced eGFR, precluding assessment of association with

CKD stages 1–2. The lack of association with higher CKD stages could possibly be explained by our stringent definition of CKD, because a kidney stone event may associate with a transient elevation in SCr not fulfilling the chronicity criterion for CKD [35].

A significant strength of this study is the large sample size and the availability of multiple SCr and urine protein measurements available for the majority of persons. To our knowledge, this is the first study to apply the KDIGO criteria in a robust fashion for identification of CKD and incidence estimation. We only included persons without evidence of CKD at baseline in this study. For these reasons, we believe that the reported incidence rates are accurate and generalizable to other Western nations, although we acknowledge the variability in CKD prevalence between populations and stress the importance of further studies with strict adherence to the KDIGO criteria for comparison.

There are, however, limitations to this study. First, the study cohort may be prone to selection bias as the inclusion of persons was based on available SCr measurements in the study period. Earlier stages of CKD may be asymptomatic and unlikely to be detected without routine screening. Although this would be the most accurate approach to incidence estimation, it is unrealistic to obtain such data for a whole nation. Since persons with available SCr measurements are likely to be less healthy than those without SCr values, the incidence rates obtained in our study may be an overestimate. Second, as SCr and urine protein measurements are included in the assessment of certain medical conditions, their association with CKD may be overestimated. Third, we used ICD diagnosis codes for identification of the majority of risk factors. For this reason, a more detailed subdivision of risk factors, for example hypertension or obesity, was not possible. In addition, ICD diagnosis codes may have been underreported.

CONCLUSION

In conclusion, we have demonstrated that the use of stringent definition yields an overall annual incidence of CKD of roughly 0.7% per year, but is higher and reaches almost 4% in the elderly. This is somewhat higher than in prior studies. The use of age-adapted eGFR thresholds results in markedly lower incidence. Risk factors for incident CKD include AKI, hypertension, diabetes and various cardiovascular diseases, as might be expected.

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AUTHORS' CONTRIBUTIONS

All authors have contributed to the study, A.J.J., B.O.E., O.S.I. and R.P. to the design and A.J.J., O.S.I. and R.P. to collection of data. A.J.J., S.H.L. and O.S.I. performed the analysis. A.J.J. wrote the initial draft and all authors have contributed to the final manuscript.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or in part, except in abstract form. Part of this work was presented at the American Society of Nephrology Kidney Week in November 2018 and at the Biennial Congress of the Nordic Society of Nephrology in September 2019.

CONFLICT OF INTEREST STATEMENT

None.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

DATA AVAILABILITY STATEMENT

Data are available upon request conditional on National Bioethics Committee approval.

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