Nephrol Dial Transplant (2023) 38: 722–732
https://doi.org/10.1093/ndt/gfac245
Advance Access publication date 25 August 2022

ORIGINAL ARTICLE

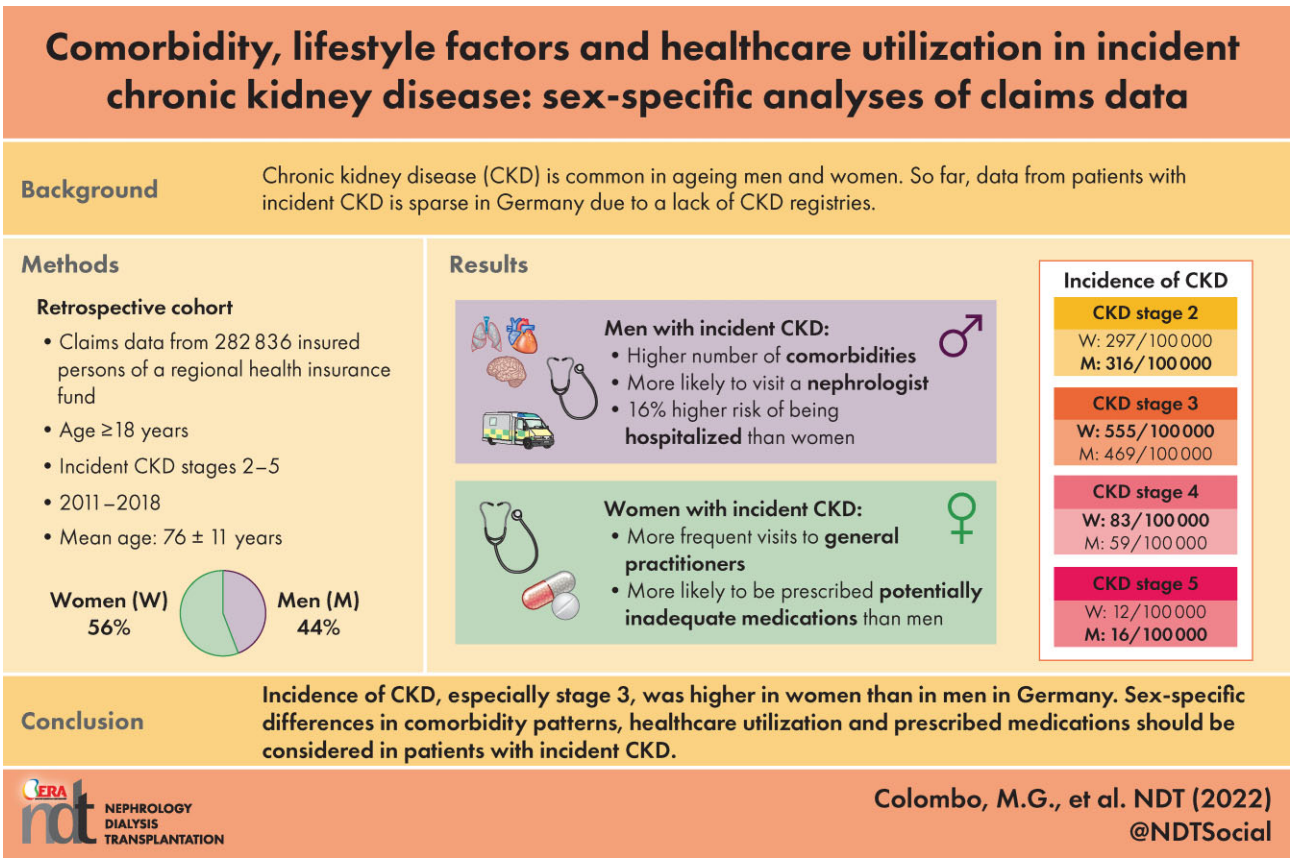
Comorbidity, life-style factors and healthcare utilization in incident chronic kidney disease: sex-specific analyses of claims data

Miriam Giovanna Colombo [1], Christian Förster [1], Stephanie Wallwiener [2], Kathrin Hassdenteufel [2], Sabine Hawighorst-Knapstein [3], Gudula Kirtschig [3], Ariane Chaudhuri [3], Simon Dally [4] and Stefanie Joos [1]

[1]Institute for General Practice and Interprofessional Care, University Hospital Tübingen, Germany, [2]Department of Obstetrics and Gynecology, University Hospital of Heidelberg, Germany, [3]Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg, Corporate division for Medical Care Design, Germany and [4]Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg, Corporate Division Control, Finances and Analytics, Germany

Correspondence to: Miriam Giovanna Colombo; E-mail: miriam.colombo@med.uni-tuebingen.de

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Chronic kidney disease (CKD) is frequently found in ageing women in men, and the incidence and prevalence of the disease is generally higher in women compared with men.
- Differences between men and women are likely due to complex interactions between biological, lifestyle as well as socio-demographic factors, and have not been fully understood.
- Germany lacks CKD registries and therefore data for patients with CKD is sparse.

What this study adds?

- Higher incidence rates of CKD stages 2–5 were found in women compared with men. The incidence of stages 3 and 4 was higher in women, while stages 2 and 5 were more often diagnosed in men.
- Men and women differed in terms of most cardiovascular, metabolic as well as renal comorbidities. Potentially inadequate medications (PIM) were more frequently prescribed in women.
- While women with incident CKD visited a general practitioner (GP) more frequently, men were more likely to visit a nephrologist and were more often hospitalized in the first year after the incident CKD diagnosis.

What impact this may have on practice or policy?

- Increased awareness is needed to avoid the use of PIMs in patients with CKD, especially in women.
- The coordination of care should be improved to ensure that patients with advanced stages of CKD get timely access to specialist care and to avoid a possible overprovision of patients with lower, uncomplicated incident CKD stages, who can be monitored and treated by a GP alone.

ABSTRACT

Background. Chronic kidney disease (CKD) is common in aging men and women. In contrast to other European countries, Germany lacks CKD registries. The aim of this study was to determine the incidence of CKD stages 2–5 in men and women in Germany. Furthermore, differences between the sexes in terms of comorbidities, potentially inappropriate medications (PIM), and healthcare utilization were examined.

Methods. In this retrospective observational study, claims data from members of a statutory health insurance fund aged 18 years or older with incident CKD between 2011 and 2018 were analyzed. Incident CKD was defined as having two confirmed diagnoses of CKD stages 2–5 from outpatient care or one primary or secondary diagnosis from inpatient care.

Results. The age- and sex-standardized incidence of all CKD stages was 945/100 000 persons between 2011 and 2018. Incident CKD, especially stages 3 and 4, occurred more frequently in women, while the incidence of stages 2 and 5 was higher in men. While women visited their GP more frequently and were prescribed PIMs more often, men were more likely to visit a nephrologist and were more often hospitalized after the incident CKD diagnosis.

Conclusion. More awareness needs to be raised towards the early detection of CKD and the use of PIMs, especially in women. Improved care coordination is needed to avoid an overprovision of patients with uncomplicated incident stages and ensure that patients with advanced CKD stages get timely access to specialist care.

Keywords: chronic kidney disease, claims data, healthcare utilization, potentially inappropriate medications, sex

INTRODUCTION

Chronic kidney disease (CKD) is mainly found in older adults and affects both men and women [1]. Even though the age-standardized prevalence of CKD has decreased in Germany by 4.7% since the 1970s [2], it is still one of the highest compared with other European countries [3].

There is growing evidence that sex (biological) and gender (socio-cultural) are important factors in the etiology, progression and therapy of CKD [4]. Previous studies found a higher prevalence of CKD in women than in men, especially in non-dialysis-dependent stages [5–7]. The disease seems to progress more rapidly in men with higher rates of renal replacement therapy and increased mortality [2, 5, 8]. Those differences are likely due to complex interactions between biological, lifestyle and socio-demographic factors and have not been fully understood [4, 7]. Disparities between the sexes in healthcare delivery and access to healthcare may contribute as modifying factors, especially in those with advanced CKD [2, 4].

Patients with CKD are at an increased risk for overall morbidity and (cardiovascular) mortality [1, 2, 9, 10]. The prevention of disease progression is the primary goal of therapy and is closely linked to early detection and adequate treatment of the underlying disease [3]. Healthcare data of patients with CKD can provide valuable knowledge to improve therapeutic management. In contrast to other European countries [11], Germany lacks CKD registries and therefore, data on the incidence of CKD are sparse.

The aim of this study was to determine the incidence of CKD stages 2–5 in men and women in Germany using claims data. A further aim was to explore possible differences between the sexes in terms of comorbidities, lifestyle factors and medications, and to analyze the utilization of in- and

outpatient healthcare in this cohort of adults with incident CKD.

MATERIALS AND METHODS

Data source and data set

In this retrospective cohort study, data from a regional statutory health insurance fund [Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg] from both outpatient and inpatient care were analyzed covering a study period from 2011 to 2018. The health insurance fund counted 4 250 889 members in 2018, corresponding to 36.6% of the inhabitants of the federal state of Baden-Württemberg.

Data were anonymized in a two-step process by the statutory health insurance fund prior to data transmission. The data set comprised socio-demographic information (age, sex, area of residence [12]), quarter and year of death, insurance time, and data from inpatient and outpatient care [International Classification of Diseases 10th revision, German modification (ICD-10-GM) codes, Anatomical Therapeutic Chemical (ATC) Classification System codes], as well as data on dialysis (hemo- and peritoneal dialysis). ICD-10-GM codes were available from both in- and outpatient care, whereas ATC codes were available from outpatient care only.

Study population

The study population comprised all members of the statutory health insurance fund, who were at least 18 years of age and had an incident diagnosis of stages 2–5 of CKD between 2011 and 2018. CKD stage 1 [glomerular filtration rate (GFR) 90 to <120 mL/min/1.73 m^2] was not included in the analysis since the coding quality of this stage is presumably poor in Germany. Stages of CKD were defined according to GFR categories proposed by the KDIGO 2012 Clinical Practice Guideline [1] and using the following ICD-10-GM codes:

- Stage 2 (GFR 60 to <90 mL/min/1.73 m^2): N18.82, N18.2
- Stage 3 (GFR 30 to <60 mL/min/1.73 m^2): N18.83, N18.3
- Stage 4 (GFR 15 to <30 mL/min/1.73 m^2): N18.84, N18.4
- Stage 5 (GFR <15 mL/min/1.73 m^2): N18.5

In contrast to the KDIGO guideline, ICD-10-GM does not differentiate between CKD stages 3a and 3b, and therefore CKD stage 3 was not further subdivided in this analysis.

A CKD diagnosis from outpatient care was recorded as an incident diagnosis if it occurred in two quarters within 1 year (M2Q criterion) and if it was a confirmed diagnosis [13]. If the M2Q criterion was met, the first quarter with a CKD diagnosis was defined as the incident quarter. In the inpatient setting, one primary or secondary diagnosis of CKD was sufficient to be counted as an incident diagnosis. When multiple stages of CKD occurred in the incident quarter, the higher stage was chosen as the incident stage. To ensure that the recorded incident diagnosis was indeed the first one, we determined a 2-year period prior to the incident diagnosis that could not contain any previous CKD diagnosis. In addition, patients with CKD had to be insured with the same statutory health insurance fund at least 2 years prior to the incident diagnosis. Patients were excluded if they had a history of kidney transplantation or received chronic dialysis (≥12 sessions of hemodialysis per quarter or one session of peritoneal dialysis) prior to the incident CKD diagnosis. An overview of all exclusion criteria is shown in Fig. 1. The final study population consisted of 282 836 men and women with incident CKD stages 2 to 5 between 2011 and 2018.

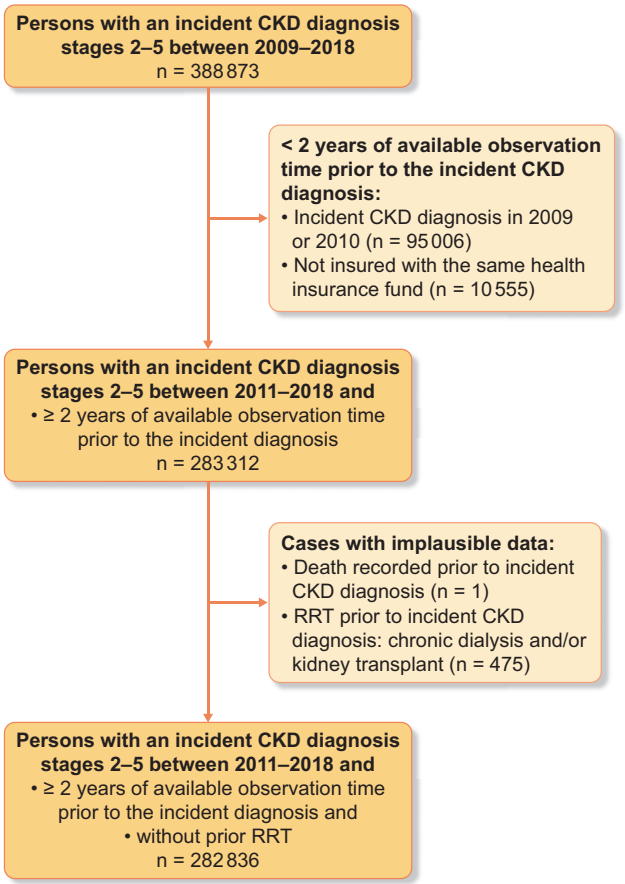


Figure 1: Flow-chart of study exclusion criteria. CKD, chronic kidney disease; RRT, renal replacement therapy.

Information on the definition of comorbidities, lifestyle factors and healthcare utilization can be found in the Supplementary materials and methods.

Statistical analysis

Differences between men and women were analyzed using Chi^2-test for nominal variables, Student's *t*-test for metric variables, and Wilcoxon–Mann–Whitney test for ordinal and non-normally distributed metric variables, respectively. The annual incidence of CKD was directly standardized according to the age and sex distribution of the German standard population in 2011 [14]. The 95% confidence intervals were calculated for the age- and sex-standardized incidence rates assuming that they follow a normal distribution.

The association between sex and the number of hospitalizations in the first year after the incident CKD diagnosis was examined using negative binomial regression. More detailed

information on the regression analysis can be found in the Supplementary materials and methods.

All statistical analyses were conducted using IBM SPSS for Windows, version 27 (IBM Corp., Armonk, NY, USA). This study was reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. Ethics approval for this study was obtained from the Ethics Committee of the University Medical Faculty and the University Hospital Tübingen (reference number: 380/2020BO).

RESULTS

Incident stages 2–5 of CKD were found in 282 836 men and women aged 18 years or older. Baseline characteristics of the study population stratified by sex and incident CKD stage are shown in Table 1 and Supplementary data, Table S1. The mean age of the whole study population was 76 years (SD ±11 years). Women made up 56% of the study population and were significantly older than men at the time of the incident diagnosis.

Incidence of CKD

The average age- and sex-standardized incidence of all CKD stages was 945/100 000 persons between 2011 and 2018. Figure 2 and Supplementary data, Table S2 show the crude and age- and sex-standardized incidence of CKD stages 2–5. With an average annual incidence of 541/100 000 persons, CKD stage 3 was the most frequent of all stages, followed by stage 2 with an average annual incidence of 313/100 000 persons. The incidence of CKD stages 4 and 5 was 77/100 000 and 14/100 000 persons, respectively (see Table 2 and Supplementary data, Table S2). Over the years, a trend towards decreasing incidence rates was observed in CKD stages 4 and 5, whereas the incidence rate of CKD stage 3 proved to be more consistent apart from a peak in 2013. The incidence rate of CKD stage 2 has increased continuously since 2012 except for 2018.

Figure 3 and Supplementary data, Table S2 show crude and age-standardized annual incidence rates of the different CKD stages stratified by sex. In general, the incidence of CKD was higher in women than men (947/100 000 women versus 860/100 000 men) between 2011 and 2018. The annual incidence rate of CKD stage 2 was higher in men than in women until a turning point in 2016, while incidence rates of stages 3 and 4 proved to be higher in women than men throughout the observation period. Incident CKD stage 5 was more often diagnosed in men than in women.

Lifestyle factors, comorbidities and potentially inappropriate medications

Further baseline characteristics of the study population are shown in Table 1 and Supplementary data, Table S1. Men and women differed significantly concerning all lifestyle factors. In general, obesity was present in approximately 30% of the study population, while the prevalence of smoking and alcohol consumption was 9% and 4%, respectively. While smoking and alcohol consumption were more prevalent in men, women were more frequently obese.

The most frequent comorbidities were hypertension, hyperlipidemia, diabetes mellitus type 2, ischemic heart disease and heart failure. Men and women differed significantly in terms of all comorbidities, except for hyperaldosteronism. The higher burden of comorbidities in men compared with women was also reflected in significantly higher values of the Charlson Comorbidity Index. In turn, women were significantly more often prescribed potentially inappropriate medications (PIMs) than men (see Supplementary data, Table S1).

Healthcare utilization

Outpatient care

Table 2 shows the utilization of outpatient care stratified by sex and incident CKD stage. Almost all men and women consulted a general practitioner (GP) at least once during the observation period. Those with incident CKD stage 5 visited a GP less often compared with the other stages. While over 90% of women and men with incident CKD stages 2–4 visited a GP in three or more quarters per year, lower frequencies were of found in those with incident CKD stage 5, especially in men.

In total, 12% of women and 18% of men sought the care of a nephrologist during the whole observation period with more visits in the higher incident CKD stages (see Table 2). The majority of men and women with incident CKD stages 2–4 visited a nephrologist in fewer than one quarter on average during the observation period, whereas 43% of men and 41% of women with incident stage 5 consulted a nephrologist every quarter over the years. The median time until the first visit to a nephrologist was one quarter in both men and women independent of the incident CKD stage (see Table 2). In general, the higher the incident CKD stage, the earlier a visit to a nephrologist.

Inpatient care

The number of hospitalizations during the first year after the incident CKD diagnosis is shown in Table 3. Statistically significant differences between the four incident stages of CKD were found in men and women. The number of hospitalizations increased with higher incident CKD stages. In general, men were hospitalized more often than women.

Supplementary data, Table S3 shows the association of sex and other predictors with the number of hospitalizations in the first year after the incident CKD diagnosis. The risk of being hospitalized was 16% lower in women compared with men (incidence rate ratio 0.841, 95% confidence interval 0.830–0.852). Independent of sex, the hospitalization rate increased with higher incident CKD stage, higher Charlson Comorbidity Index score as well as increasing number of PIMs.

DISCUSSION

To our knowledge, this is the first study to determine the incidence of CKD in the German population. Previous studies from Germany focused solely on CKD prevalence [15–19].

Table 1: Baseline characteristics of adults with incident CKD between 2011 and 2018 stratified by sex and incident stage ($n = 282\,836$).

	Women					Men				
	Total $n = 158\,727$	CKD stage 2 $n = 47\,848$	CKD stage 3 $n = 94\,457$	CKD stage 4 $n = 14\,463$	CKD stage 5 $n = 1959$	Total $n = 124\,109$	CKD stage 2 $n = 44\,171$	CKD stage 3 $n = 68\,902$	CKD stage 4 $n = 8818$	CKD stage 5 $n = 2218$
Socio-demographic characteristics										
Age, years, mean ± SD	78 ± 11	74 ± 12	80 ± 10	81 ± 10	75 ± 14	74 ± 11	71 ± 12	76 ± 11	77 ± 12	70 ± 11
Area of residence										
Peripheral area	45 124 (28.4)	13 987 (29.2)	26 525 (28.1)	4056 (28.0)	556 (28.4)	35 399 (28.5)	13 199 (29.9)	19 057 (27.7)	2539 (28.8)	604 (27.2)
Intermediate area	53 645 (33.8)	16 127 (33.7)	31 880 (33.8)	4998 (34.6)	640 (32.7)	40 492 (32.6)	14 407 (32.6)	22 452 (32.6)	2937 (31.4)	696 (31.4)
Central area	59 511 (37.5)	17 605 (36.8)	35 784 (37.9)	5371 (37.1)	751 (38.3)	47 722 (38.5)	16 388 (37.1)	27 120 (39.4)	3311 (37.5)	903 (40.7)
Not specified	447 (0.3)	129 (0.3)	268 (0.3)	28 (0.3)	12 (0.6)	496 (0.4)	177 (0.4)	273 (0.4)	31 (0.4)	15 (0.7)
Lifestyle factors										
Smoking[a]	8634 (5.4)	3192 (6.7)	4689 (5.0)	636 (4.4)	117 (6.0)	16 185 (13.0)	6110 (13.8)	8693 (12.6)	1064 (12.1)	318 (14.3)
Obesity[a]	50 332 (31.7)	15 149 (31.7)	30 239 (32.0)	4365 (30.2)	574 (29.6)	34 614 (27.9)	12 579 (28.5)	19 280 (28.0)	2218 (25.2)	537 (24.2)
Alcohol[a]	3084 (1.9)	906 (1.9)	1822 (1.9)	286 (2.0)	70 (3.6)	9392 (7.6)	3166 (7.2)	5249 (7.6)	737 (8.4)	240 (10.8)
History of disease/comorbidities										
Diabetes mellitus										
Type 1	522 (0.3)	200 (0.4)	261 (0.3)	53 (0.4)	8 (0.4)	507 (0.4)	217 (0.5)	250 (0.4)	30 (0.3)	10 (0.5)
Type 2	74 688 (47.1)	20 559 (43.0)	45 713 (48.4)	7484 (51.7)	932 (47.6)	60 183 (48.5)	20 396 (46.2)	34 473 (50.0)	4307 (48.8)	1007 (45.4)
Hyperlipidemia	92 470 (58.3)	27 618 (57.7)	55 967 (59.3)	7955 (55.0)	930 (47.5)	73 934 (59.6)	26 462 (59.9)	41 671 (60.5)	4716 (53.5)	1085 (48.9)
Hypertension	143 414 (90.4)	40 740 (85.1)	87 565 (92.7)	13 419 (92.9)	1680 (85.8)	108 128 (87.1)	37 056 (83.9)	61 570 (89.4)	7745 (87.8)	1757 (79.2)
Stroke	19 351 (12.2)	4914 (10.3)	12 361 (13.1)	1887 (13.0)	189 (9.6)	16 186 (13.0)	4996 (11.3)	9827 (14.3)	1143 (13.0)	220 (9.9)
Ischemic heart disease	52 875 (33.3)	13 277 (27.7)	33 803 (35.8)	5238 (36.2)	557 (28.4)	53 581 (43.2)	17 255 (39.1)	31 819 (46.2)	3766 (42.7)	741 (33.4)
Heart failure	60 747 (38.3)	13 773 (28.8)	39 322 (41.6)	6928 (47.9)	724 (37.0)	44 418 (35.8)	12 775 (38.9)	27 318 (39.6)	3640 (41.3)	685 (30.9)
Atrial fibrillation/flutter	38 918 (24.5)	8503 (17.8)	25 774 (27.3)	4200 (29.0)	441 (22.5)	31 572 (25.4)	9081 (20.6)	19 597 (28.4)	2438 (27.6)	456 (20.6)
PAD	25 292 (15.3)	6103 (12.8)	15 417 (16.3)	2485 (17.2)	287 (14.7)	28 379 (22.9)	8684 (19.7)	17 087 (24.8)	2127 (24.1)	481 (21.7)
Acute renal failure	389 (0.2)	72 (0.2)	235 (0.2)	66 (0.5)	16 (0.8)	426 (0.3)	104 (0.2)	258 (0.4)	44 (0.5)	20 (0.9)
Glomerulonephritis	5960 (3.8)	1554 (3.2)	3625 (3.8)	704 (4.9)	77 (3.9)	5927 (4.8)	1816 (4.1)	3543 (5.1)	473 (5.4)	95 (4.3)
Nephritic syndrome	824 (0.5)	247 (0.5)	426 (0.5)	116 (0.8)	35 (1.8)	872 (0.7)	292 (0.7)	417 (0.6)	120 (1.4)	43 (1.9)
Nephrotic syndrome	291 (0.2)	84 (0.2)	135 (0.1)	58 (0.4)	14 (0.7)	370 (0.3)	105 (0.2)	175 (0.3)	64 (0.7)	26 (1.2)
Tubulointerstitial nephritis	2476 (1.6)	749 (1.6)	1453 (1.5)	233 (1.6)	41 (2.1)	1096 (0.9)	382 (0.9)	382 (0.9)	597 (0.9)	89 (1.0)
Polycystic kidney disease	507 (0.3)	155 (0.3)	281 (0.3)	58 (0.4)	13 (0.7)	630 (0.5)	221 (0.5)	340 (0.5)	52 (0.6)	17 (0.8)
Amyloidosis	184 (0.1)	33 (0.1)	117 (0.1)	22 (0.2)	12 (0.6)	225 (0.2)	52 (0.1)	141 (0.2)	25 (0.3)	7 (0.3)
Affective mood disorders	59 373 (37.4)	18 060 (37.7)	35 580 (37.7)	5093 (35.2)	640 (32.7)	26 476 (21.3)	9599 (21.7)	14 706 (21.3)	1764 (20.0)	407 (18.3)
Dementia	10 391 (6.5)	2468 (5.2)	6710 (7.1)	1119 (7.7)	94 (4.8)	5908 (4.8)	1780 (4.0)	3529 (5.1)	510 (5.8)	89 (4.0)
Rheumatologic disease	23 219 (14.6)	6892 (14.4)	14 105 (14.9)	1965 (13.6)	257 (13.1)	12 690 (10.2)	4208 (9.5)	7289 (10.6)	966 (11.0)	227 (10.2)
Hyperaldosteronism	337 (0.2)	77 (0.2)	223 (0.2)	25 (0.2)	2 (0.1)	300 (0.2)	90 (0.2)	175 (0.3)	30 (0.3)	5 (0.2)
Thyroid disease	68 082 (43)	21 589 (45)	40 158 (43)	5627 (39)	708 (36)	26 184 (21)	9363 (21)	14 730 (21)	1703 (19)	388 (18)
Hyperuricemia	31 513 (20)	7238 (15)	20 148 (21)	3688 (26)	439 (22)	35 747 (29)	11 114 (25)	21 285 (31)	2749 (31)	599 (27)
Chronic obstructive lung disease	34 161 (22)	10 042 (21)	20 697 (22)	3050 (21)	372 (19)	32 710 (26)	10 973 (25)	18 885 (27)	2342 (27)	510 (23)
Chronic liver disease	19 682 (12)	6024 (13)	11 680 (12)	1654 (11)	254 (13)	20 873 (17)	7444 (17)	11 560 (17)	1479 (17)	390 (18)
Acute viral hepatitis	615 (0.4)	205 (0.4)	351 (0.4)	49 (0.3)	10 (0.5)	638 (0.5)	213 (0.5)	365 (0.5)	43 (0.5)	26 (1)
HIV/AIDs	109 (0.1)	33 (0.1)	61 (0.1)	13 (0.1)	2 (0.1)	197 (0.2)	71 (0.2)	105 (0.2)	5 (0.1)	16 (0.7)
IBD	1661 (1)	539 (1)	963 (1)	135 (0.9)	25 (1)	1434 (1)	538 (1)	771 (1)	100 (1)	25 (1)
Any malignancies	34 586 (22)	9683 (20)	21 222 (23)	3247 (23)	434 (22)	36 001 (29)	11 252 (26)	21 335 (31)	2832 (32)	582 (26)
Multiple myeloma	516 (0.3)	111 (0.2)	282 (0.3)	95 (0.7)	28 (1)	497 (0.4)	114 (0.3)	304 (0.4)	52 (0.6)	27 (1)

Data are presented as *n* (%) unless otherwise indicated.

[a]Smoking: ICD-10 code F17 (behavioral disorders due to smoking); obesity: ICD-10 codes E65, E66, E67, E68; alcohol: ICD-10 code F10 (behavioral disorders due to alcohol).

HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICD-10, International Classification of Diseases 10th revision.

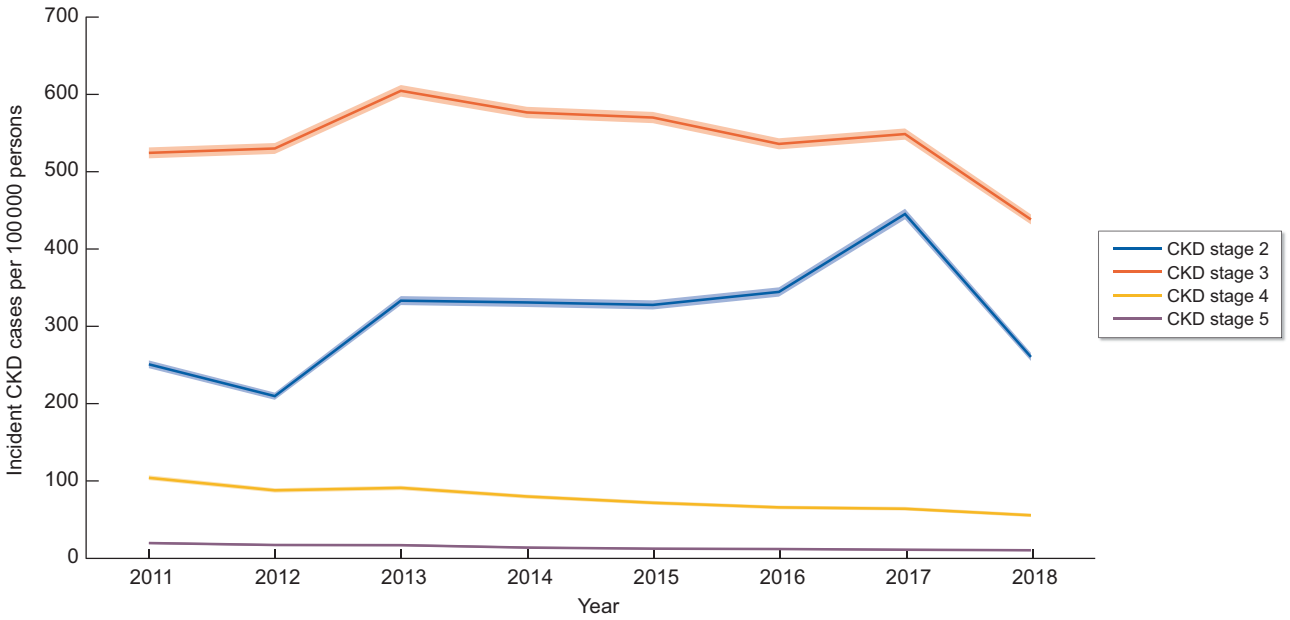


Figure 2: Age- and sex-standardized incidence of chronic kidney disease in adults between 2011 and 2018. The 95% confidence intervals are presented as transparent areas behind each curve.

The age- and sex-standardized annual incidence of CKD was 945/100 000 persons and a higher incidence rate of CKD stages 2–5 was found in women than men, with CKD stage 3 as the most frequently diagnosed stage among both sexes. The incidence of stages 3 and 4 proved to be higher in women, while stages 2 and 5 were more often diagnosed in men. Statistically significant differences between the sexes were found in almost all comorbidities, and PIMs were more frequently prescribed in women. While women visited a GP more frequently, men were more likely to visit a nephrologist and were more often hospitalized in the first year after the incident CKD diagnosis.

Incidence of CKD

CKD is a common diagnosis in older adults [20, 21], which was also reflected in our study population. Previous studies reported varying incidence rates of CKD. With 170/100 000 population, a study from the UK with a similar median age reported a lower annual incidence rate compared with our study [20]. The Framingham Offspring study found incident kidney disease in 9400/100 000 of their community-based cohort with a mean age of 43 years [22]. A study in 3313 Iranian adults (≥20 years) reported an annual incidence of CKD stages 3–5 of more than 2000/100 000 [23], which is high compared with our results. Differences between previous studies and our study are likely due to different definitions or diagnostic criteria of CKD and deviating inclusion criteria.

Sex differences

Sex differences in the etiology, epidemiology and prognosis of CKD are well established in the literature [5–7, 24–27]. In line with our results, a Japanese study reported an annual incidence of CKD stage 3 or above that was lower in men (800/100 000) compared with women (1500/100 000) [28]. In contrast, Drey and colleagues found higher annual incidence rates of CKD among men in all age groups, especially those aged 80 years and older [20].

CKD, especially stage 2, is typically asymptomatic and mainly identified through routine check-ups or as incidental finding [29]. Men in our study population had a higher burden of comorbidities than women at the time of incident CKD diagnosis, which might have increased their chances of being incidentally diagnosed with CKD stage 2. In turn, women in our study population were significantly older at the time of the incident diagnosis. The fact that kidney function declines physiologically (and mostly asymptomatically) with age combined with a lower burden of comorbidities and higher life expectancy [6] might explain the higher incidence of CKD stages 3 and 4 in women in our study population [30].

Comorbidities and medications

Comorbidities and previous acute diseases were frequently found in our cohort of men and women with CKD. The most common causes of CKD in high- and middle-income countries are hypertension and diabetes mellitus [21]. Hypertension and heart failure were more often found in women in our study cohort, whereas other cardiovascular diseases and diabetes mellitus were more frequently diagnosed in men. In contrast to these frequent causes of CKD, rarer diseases such as polycystic kidney disease, amyloidosis and multiple myeloma were more frequently found in higher CKD stages, as well as nephritic and nephrotic syndrome as signs of glomerular damage. This could result from a more rapid deterioration of kidney function in patients with these diseases. Patients with polycystic kidney disease, for example, are known to experience a varying but fast GFR decline over the years [31]. In a meta-analysis

Table 2: Utilization of outpatient care in adults with incident chronic kidney disease stratified by sex and incident stage ($n = 209\,498$).

	Women						Men						
	Total	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	*P*-value	Total	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	*P*-value	*P*-value
No visit to nephrologist	103 735 (88)	35 830 (92)	61 077 (88)	6339 (73)	489 (46)	<.001[a]	74 979 (82)	31 764 (89)	39 754 (81)	2973 (60)	488 (38)	<.001[a]	<.001[a]
Visit to nephrologist	14.504 (12)	3.017 (8)	8.521 (12)	2.389 (27)	577 (54)		16 290 (18)	3928 (11)	9542 (19)	2026 (41)	784 (62)		
Time to 1st visit to nephrologist in quarters, median (IQR)	1 (0–6)	1 (0–7)	1 (0–7)	0 (0–4)	0 (0–1)	<.001[b]	1 (0–6)	1 (0–8)	1 (0–7)	0 (0–3)	0 (0–0)	<.001[b]	<.585[c]
Frequency of visits to nephrologist in quarters/year[d]						<.001[b]						<.001[b]	<.001[c]
<1 quarter/year	7104 (49)	1633 (54)	4528 (53)	842 (35)	101 (18)		7467 (46)	2148 (55)	4647 (49)	531 (26)	141 (18)		
1–<2 quarters/year	3659 (25)	812 (27)	2192 (26)	575 (24)	80 (14)		4143 (25)	978 (25)	2573 (27)	495 (24)	97 (12)		
2–<3 quarters/year	1947 (13)	349 (12)	1077 (13)	456 (19)	65 (11)		2268 (14)	504 (13)	1303 (14)	386 (19)	75 (10)		
3–<4 quarters/year	1132 (8)	158 (5)	528 (6)	352 (15)	94 (16)		1518 (9)	212 (5)	769 (8)	401 (20)	136 (14)		
4 quarters/year	662 (5)	65 (2)	196 (2)	164 (7)	237 (41)		884 (5)	86 (2)	250 (3)	213 (11)	335 (43)		
No visit to GP	176 (0.1)	38 (0.1)	115 (0.2)	16 (0.2)	7 (0.7)	<.001[a]	199 (0.2)	63 (0.2)	114 (0.2)	13 (0.03)	9 (0.7)	<.001[a]	<.001[a]
Visit to GP	118 063 (100)	38 809 (100)	69 483 (100)	8712 (100)	1059 (99)		91 060 (100)	35 629 (100)	49 182 (100)	4986 (100)	1263 (99)		
Frequency of visits to GP in quarters/year[d]						<.001[b]						<.001[b]	<.001[c]
<1 quarter/year	479 (0.4)	168 (0.4)	249 (0.4)	38 (0.4)	24 (2)		576 (0.6)	234 (0.7)	269 (0.5)	41 (0.8)	32 (3)		
1–<2 quarters/year	900 (0.8)	371 (1)	426 (0.6)	68 (0.8)	35 (3)		1159 (1)	498 (1)	511 (1)	86 (2)	64 (5)		
2–<3 quarters/year	1962 (2)	897 (2)	910 (1)	114 (1)	41 (4)		2375 (3)	1149 (3)	992 (2)	139 (3)	95 (8)		
3–<4 quarters/year	11 291 (10)	4592 (12)	5891 (9)	684 (8)	124 (12)		11 096 (12)	4863 (14)	5440 (11)	590 (12)	203 (16)		
4 quarters/year	103 431 (88)	32 781 (85)	62 007 (89)	7808 (90)	835 (79)		75 854 (83)	28 885 (81)	41 970 (85)	4130 (83)	869 (69)		

Data are presented as *n* (%) unless otherwise indicated.

[a]Chi^2-test was used to test for differences between the 4 CKD stages and between men and women.

[b]Kruskall–Wallis test was used to test for differences between CKD stages.

[c]Wilcoxon–Mann–Whitney test was used to test for differences between men and women.

[d]Total number of quarters with a visit divided by observation time in years.

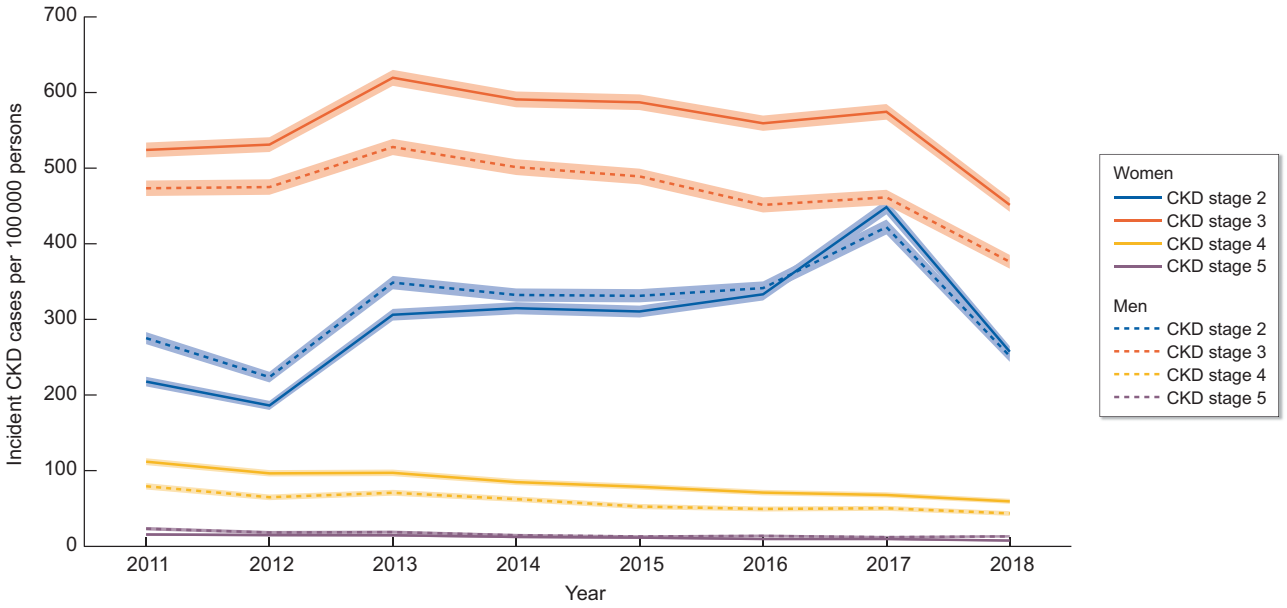


Figure 3: Age-standardized incidence of chronic kidney disease in adults between 2011 and 2018 stratified by sex. The 95% confidence intervals are presented as transparent areas behind each the curve.

containing data from 11 345 patients, the authors concluded that especially men with non-diabetic CKD experienced faster disease progression than women [32]. Differences between the sexes in terms of comorbidities might also be attributed to women being significantly older than men at the time of the incident CKD diagnosis.

Interestingly, women aged 65 years and older were more prone to being prescribed PIMs across all CKD stages than men. Since the kidney plays an important role in the pharmacokinetics of various medications, prescribing PIMs in patients with impaired kidney function might have detrimental effects. In line with our results, a study in 6392 patients with CKD identified female sex as a predictor for the use of kidney-based PIM [33]. A recent cross-sectional study using Medicare data found that the odds of women with CKD receiving PIMs were 1.25 times higher than men [34]. Therefore, medications that are taken on a regular basis should be re-evaluated by both GPs and nephrologists when (female) patients aged 65 years or older are diagnosed with CKD.

Inpatient and outpatient care

After being diagnosed with incident CKD, 12% of women and 18% of men in our study population were seen by a nephrologist. This proportion increased with higher incident CKD stages. These results are consistent with previous studies that reported significant associations of male sex, younger age and lower estimated GFR with both prior contact with a nephrologist and referral to a nephrologist, respectively [35, 36]. Referral to a nephrologist is advised in patients with a GFR <30 mL/min/1.73 m^2 in current clinical practice guidelines [1], and accordingly, those with incident CKD stages 4 and 5 visited a nephrologist earlier after the incident diagnosis and more frequently than those with lower incident stages in our study population. Previous studies have shown that early nephrologist referral was associated with improved outcomes in patients with more advanced pre-dialysis CKD [36, 37]. The Chronic Renal Insufficiency Cohort study evaluated whether patients with mild to moderate CKD also benefited from referrals to specialists. They concluded that study participants who had prior contact with a nephrologist were more likely to be treated for CKD complications even though there was no statistically significant association with estimated GFR loss >50%, incident cardiovascular disease and death [35]. The guideline of the German College of General Practitioners and Family Physicians recommends basing the decision for the referral to a nephrologist depending on age, comorbidities, general health condition and preference of the patient, in addition to a reduced GFR [38]. This approach could avoid possible overprovision of patients with less complicated CKD and less advanced CKD stages, who can be treated by their GP alone. Nevertheless, the association between early and regular visits to nephrologists and long-term outcomes in men and women with CKD needs further investigation.

Men were more frequently hospitalized in the first year after the incident CKD diagnosis than women, and male sex remained a statistically significant predictor of the number of hospitalizations after adjusting for other factors. A possible explanation for higher hospitalization rates among men could be that kidney function declines faster in men than in women with CKD, requiring inpatient treatment [5–7]. Additionally, previous studies have shown that men with CKD were more likely to receive renal replacement therapy and suffer from cardiovascular events [39, 40], which could result in more hospital stays. Since we only analyzed hospitalizations due to all causes, we cannot make inferences about the reasons for the hospital stays in our study. A previous cohort study found that cardiovascular, genitourinary, digestive, endocrine, nutritional or metabolic, and respiratory causes were the most frequent among patients with CKD [41].

Table 3: Utilization of inpatient care in adults with incident chronic kidney disease stratified by sex and incident stage ($n = 209\,498$).

	Women						Men					
	Total	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	*P*-value[a]	Total	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	*P*-value[a]
Number of hospitalizations during the 1st year, *n* (%)						<.001						<.001
No hospitalization during the 1st year	66 630 (56)	24 772 (64)	37 249 (54)	4180 (48)	429 (40)		49 096 (54)	21 620 (61)	24 853 (50)	2165 (43)	458 (36)	
1 hospitalization	26 274 (22)	7626 (20)	16 252 (23)	2146 (25)	250 (24)		19 591 (22)	7061 (20)	11 109 (23)	1162 (23)	259 (20)	
2 hospitalizations	12 439 (11)	3366 (8)	7939 (11)	1095 (13)	139 (13)		10 062 (11)	3293 (9)	5872 (12)	694 (14)	203 (16)	
3 hospitalizations	6277 (5)	1618 (4)	3968 (6)	606 (10)	85 (8)		5402 (6)	1647 (5)	3214 (7)	414 (8)	127 (10)	
4 hospitalizations	3107 (3)	747 (2)	1965 (3)	338 (4)	57 (5)		3068 (3)	914 (3)	1815 (4)	249 (5)	90 (7)	
5 hospitalizations	1547 (1)	374 (1)	981 (1)	151 (2)	43 (4)		1689 (2)	490 (1)	1028 (2)	123 (3)	48 (4)	
≥6 hospitalizations	1965 (2)	446 (1)	1244 (2)	212 (2)	63 (6)		2351 (3)	667 (2)	1405 (3)	192 (4)	87 (7)	

[a]Kruskal–Wallis test was used to test for differences between the four CKD stages in women and men.
[b]Wilcoxon–Mann–Whitney test was used to test for differences between men and women.

Limitations

Claims data have been increasingly used for research purposes in recent years because they offer the opportunity to generate knowledge from comparatively large study cohorts. However, their use entails several limitations [42, 43] since this kind of data collection is not originally intended for research purposes but for the billing of health services.

In our study cohort, CKD incidence decreased in both men and women in 2018. This decrease can be explained by missing incident CKD cases from outpatient care for the fourth quarter of 2018. Diagnoses from outpatient care were only counted as incident if the M2Q criterium was satisfied, which entails the presence of a CKD diagnosis in two quarters within 1 year. Since the data set only contained reliable data until the fourth quarter of 2018, those who would have had an incident diagnosis from outpatient care in this last quarter were not represented in our data set.

Since there were no data available before 2009, we could not determine whether men and women might have had any earlier incident CKD diagnosis. We tried to minimize this potential bias by introducing a pre-observation period of 2 years, which could not contain previous CKD diagnoses. Nevertheless, we cannot completely rule out that CKD was already present previously.

Finally, we did not include patients with incident CKD stage 1 into our study population since the coding quality of this stage of CKD is presumably poor in Germany. Therefore, our results cannot be generalized to patients with incident CKD stage 1.

In conclusion, this study provides valuable insights into the epidemiology of CKD and the healthcare utilization in patients with CKD with a focus on sex-specific differences. Even though the incidence of more advanced stages of CKD seemed to decrease slightly over the years, more awareness needs to be raised towards the early detection of the disease. Increased awareness is also needed to avoid the use of PIMs in patients with CKD, especially in women. Additionally, we call for better coordination of care to ensure that patients with advanced stages of CKD get timely access to specialist care and to avoid a possible overprovision of patients with lower, uncomplicated incident CKD stages, who can be monitored and treated by a GP alone.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

The Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg kindly provided data for the analyses. We would like to thank Dr Hannah Fuhr for language editing the manuscript.

FUNDING

This study was funded by the Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg. The funders had no role in study

design and analysis, decision to publish or drafting of the manuscript.

AUTHORS' CONTRIBUTIONS

M.G.C. designed the study, analyzed the data and wrote the manuscript. C.F. designed the study, and contributed to the interpretation of the results and the writing of the manuscript. S.W., K.H., S.H.-K., G.K. and A.C. gave input from their field of knowledge for the design of the study and the interpretation of the results and revised the manuscript. S.D. provided the data, contributed to the selection of the study cohort and revised the manuscript. S.J. is the project leader, designed the study and contributed to the interpretation of the results and the writing of the manuscript. All authors revised and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg under license and are not publicly available. Data are available upon reasonable request to the corresponding author with permission of AOK Baden-Württemberg.

CONFLICT OF INTEREST STATEMENT

This study was conducted as part of a joint project of the Allgemeine Ortskrankenkasse (AOK) Baden-Württemberg and the Institute for General Practice and Interprofessional Care of the University Hospital Tübingen. In the framework of this joint project M.G.C., C.F. and S.J. received funding from the AOK Baden-Württemberg. In the past 36 months, S.W. received a grant from the Federal Joint Committee (G-BA) Innovation Fund, consulting fees from TK health insurance (Techniker Krankenkasse) and participated in the Advisory Board of Digital Women's Health. All other authors have no conflict of interest to declare.

REFERENCES

1. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members (KDIGO). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013;**158**:825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;**395**:709–33. https://doi.org/10.1016/S0140-6736(20)30045-3
3. Bruck K, Stel VS, Gambaro G *et al.* CKD prevalence varies across the European general population. *J Am Soc Nephrol* 2016;**27**:2135–47. https://doi.org/10.1681/ASN.2015050542
4. Bairey Merz CN, Dember LM, Ingelfinger JR *et al.* Sex and the kidneys: current understanding and research opportunities. *Nat Rev Nephrol* 2019;**15**:776–83. https://dx.doi.org/10.1038/s41581-019-0208-6
5. Neugarten J, Golestaneh L. Influence of sex on the progression of chronic kidney disease. *Mayo Clin Proc* 2019;**94**:1339–56. https://doi.org/10.1016/j.mayocp.2018.12.024
6. Carrero JJ, Hecking M, Chesnaye NC *et al.* Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018;**14**:151–64. https://doi.org/10.1038/nrneph.2017.181
7. Cobo G, Hecking M, Port FK *et al.* Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)* 2016;**130**:1147–63. https://doi.org/10.1042/CS20160047
8. Herget-Rosenthal S, Dehnen D, Kribben A *et al.* Progressive chronic kidney disease in primary care: modifiable risk factors and predictive model. *Prev Med* 2013;**57**:357–62. https://doi.org/10.1016/j.ypmed.2013.06.010
9. Hill NR, Fatoba ST, Oke JL *et al.* Global prevalence of chronic kidney disease - A systematic review and meta-analysis. *PLoS One* 2016;**11**:e0158765. https://doi.org/10.1371/journal.pone.0158765
10. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR *et al.* Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–52. https://doi.org/10.1016/S0140-6736(13)60595-4
11. Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) registry annual report 2016: a summary. *Clin Kidney J* 2019;**12**:702–20. https://doi.org/10.1093/ckj/sfz011
12. *The Federal Office for Building and Regional Planning (BBR)*. Regional planning report. Bonn: BBR; 2005, 20.
13. Roessler T, Zschocke J, Roehrig A *et al.* Administrative prevalence and incidence, characteristics and prescription patterns of patients with migraine in Germany: a retrospective claims data analysis. *J Headache Pain* 2020;**21**:85. https://doi.org/10.1186/s10194-020-01154-x
14. The Federal Health Monitoring System (GBE). *Standard populations used for age standardization in the information system of the Federal Health Monitoring. Classification: age, sex, type of standard population.* https://www.gbe-bund.de/gbe/pkg_isgbe5.prc_menu_olap?p_uid=gast&p_aid=18290546&p_sprache=E&p_help=3&p_indnr=1000&p_indsp=&p_ityp=H&p_fid= (28 July 2021, date last accessed).
15. Gergei I, Klotsche J, Woitas RP *et al.* Chronic kidney disease in primary care in Germany. *J Public Health Heidelberg* 2017;**25**:223–30. https://doi.org/10.1007/s10389-016-0773-0
16. Girndt M, Trocchi P, Scheidt-Nave C *et al.* The prevalence of renal failure. Results from the German Health Interview and Examination Survey for Adults, 2008-2011 (DEGS1). *Dtsch Arztebl Int* 2016;**113**:85–91.
17. Aumann N, Baumeister SE, Rettig R *et al.* Regional variation of chronic kidney disease in Germany: results from two population-based surveys. *Kidney Blood Press Res* 2015;**40**:231–43. https://doi.org/10.1159/000368499
18. Rothenbacher D, Klenk J, Denkinger M *et al.* Prevalence and determinants of chronic kidney disease in community-dwelling elderly by various estimating equations. *BMC Public Health* 2012;**12**:343. https://doi.org/10.1186/1471-2458-12-343
19. Zhang QL, Koenig W, Raum E *et al.* Epidemiology of chronic kidney disease: results from a population of older adults in Germany. *Prev Med* 2009;**48**:122–7. https://doi.org/10.1016/j.ypmed.2008.10.026
20. Drey N, Roderick P, Mullee M *et al.* A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003;**42**:677–84. https://doi.org/10.1016/S0272-6386(03)00916-8
21. Webster AC, Nagler EV, Morton RL *et al.* Chronic kidney disease. *Lancet* 2017;**389**:1238–52. https://doi.org/10.1016/S0140-6736(16)32064-5
22. Fox CS, Larson MG, Leip EP *et al.* Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004;**291**:844–50.https://doi.org/10.1001/jama.291.7.844
23. Tohidi M, Hasheminia M, Mohebi R *et al.* Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort. *PLoS One* 2012;**7**:e45304. https://doi.org/10.1371/journal.pone.0045304
24. Carrero JJ. Gender differences in chronic kidney disease: underpinnings and therapeutic implications. *Kidney Blood Press Res* 2010;**33**:383–92. https://doi.org/10.1159/000320389
25. Goldberg I, Krause I. The role of gender in chronic kidney disease. *EMJ* 2016;**1**:58–64.
26. Lima-Posada I, Portas-Cortes C, Perez-Villalva R *et al.* Gender differences in the acute kidney injury to chronic kidney disease transition. *Sci Rep* 2017;**7**:12270. https://doi.org/10.1038/s41598-017-09630-2
27. Ricardo AC, Yang W, Sha D *et al.* Sex-related disparities in CKD progression. *J Am Soc Nephrol* 2019;**30**:137–46. https://doi.org/10.1681/ASN.2018030296

28. Yamagata K, Ishida K, Sairenchi T *et al.* Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007;**71**:159–66. https://doi.org/10.1038/sj.ki.5002017
29. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA* 2019;**322**:1294–304. https://doi.org/10.1001/jama.2019.14745
30. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis* 2016;**23**:19–28. https://doi.org/10.1053/j.ackd.2015.08.004
31. Brosnahan GM, Abebe KZ, Moore CG *et al.* Patterns of kidney function decline in autosomal dominant polycystic kidney disease: a post hoc analysis from the HALT-PKD trials. *Am J Kidney Dis* 2018;**71**:666–76. https://doi.org/10.1053/j.ajkd.2017.10.023
32. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000;**11**:319–29. https://doi.org/10.1681/ASN.V112319
33. Secora A, Alexander GC, Ballew SH *et al.* Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults. *Drugs Aging* 2018;**35**:735–50. https://doi.org/10.1007/s40266-018-0563-1
34. Silva-Almodovar A, Hackim E, Wolk H *et al.* Potentially inappropriately prescribed medications among Medicare medication therapy management eligible patients with chronic kidney disease: an observational analysis. *J Gen Intern Med* 2021;**36**:2346–52. https://doi.org/10.1007/s11606-020-06537-z
35. Ricardo AC, Roy JA, Tao K *et al.* Influence of nephrologist care on management and outcomes in adults with chronic kidney disease. *J Gen Intern Med* 2016;**31**:22–9. https://doi.org/10.1007/s11606-015-3452-x
36. Liu P, Quinn RR, Karim ME *et al.* Nephrology consultation and mortality in people with stage 4 chronic kidney disease: a population-based study. *CMAJ* 2019;**191**:E274–82. https://doi.org/10.1503/cmaj.181372
37. Smart NA, Dieberg G, Ladhani M *et al.* Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014;CD007333.
38. Weckmann G, Chenot JF, Stracke S. The management of non-dialysis-dependent chronic kidney disease in primary care. *Dtsch Arztebl Int* 2020;**117**:745–51.
39. Fernandez-Prado R, Fernandez-Fernandez B, Ortiz A. Women and renal replacement therapy in Europe: lower incidence, equal access to transplantation, longer survival than men. *Clin Kidney J* 2018;**11**:1–6. https://doi.org/10.1093/ckj/sfx154
40. Major RW, Cheng MRI, Grant RA *et al.* Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One* 2018;**13**:e0192895. https://doi.org/10.1371/journal.pone.0192895
41. Schrauben SJ, Chen HY, Lin E *et al.* Hospitalizations among adults with chronic kidney disease in the United States: a cohort study. *PLoS Med* 2020;**17**:e1003470. https://doi.org/10.1371/journal.pmed.1003470
42. Neubauer S, Kreis K, Klora M *et al.* Access, use, and challenges of claims data analyses in Germany. *Eur J Health Econ* 2017;**18**:533–6. https://doi.org/10.1007/s10198-016-0849-3
43. Kreis K, Neubauer S, Klora M *et al.* Status and perspectives of claims data analyses in Germany-A systematic review. *Health Policy* 2016;**120**:213–26. https://doi.org/10.1016/j.healthpol.2016.01.007

Received: 4.5.2022; Editorial decision: 3.8.2022