ORIGINAL ARTICLE

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Inherited kidney disease and CAKUT are common causes of kidney failure requiring kidney replacement therapy: an ERA Registry study

Alberto Ortiz[1,2,*], Anneke Kramer[3,4,*], Gema Ariceta[5,6], Olga L. Rodríguez Arévalo[7,8], Ann C. Gjerstad[9], Carmen Santiuste[10,11], Sara Trujillo-Alemán[12], Pietro Manuel Ferraro[13], Shona Methven[14], Rafael Santamaría[15,16], Radomir Naumovic[17,18], Halima Resic[19], Kristine Hommel[20], Mårten Segelmark[21,22], Patrice M. Ambühl[23], Søren S. Sorensen[24], Cyrielle Parmentier[25], Enrico Vidal[26], Sevcan A. Bakkaloglu[27], Lucy Plumb[28,29], Runolfur Palsson[30,31], Julia Kerschbaum[32], Marc A. G. J. ten Dam[33,34], Vianda S. Stel[3,4], Kitty J. Jager[3,4] and Roser Torra[35]

[1]Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain
[2]Department of Medicine, Universidad Autonoma de Madrid, Madrid, Spain
[3]ERA Registry, Amsterdam UMC location University of Amsterdam, Medical Informatics, Amsterdam, The Netherlands
[4]Amsterdam Public Health Research Institute, Quality of Care, Amsterdam, The Netherlands
[5]Department of Pediatric Nephrology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[6]Department of Pediatrics, Autonomous University of Barcelona, Barcelona, Spain
[7]Registry of Renal Patients of the Valencian Community, General Directorate of Public Health and Addictions, Ministry of Universal Health and Public Health, Valencia, Spain
[8]Health and Well-being Technologies Program, Polytechnic University of Valencia, Valencia, Spain
[9]Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[10]Murcia Renal Registry, Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain
[11]CIBER Epidemiología y Salud Pública, Madrid, Spain
[12]Health Quality Assessment and Information System Service, Dirección General de Programas Asistenciales, Servicio Canario de la Salud, Las Palmas de Gran Canaria, Spain
[13]Section of Nephrology, Department of Medicine, Università degli Studi di Verona, Verona, Italy
[14]Department of Renal Medicine, Aberdeen Royal Infirmary, Foresterhill Health Campus, Aberdeen, UK
[15]Andalusian Autonomous Transplant Coordination Information System, Seville, Spain
[16]Nephrology Service, Reina Sofia University Hospital, Cordoba, Spain
[17]Clinical Department of Nephrology, Metabolic Disorders and Dialysis, Zvezdara Clinical Hospital, Belgrade, Serbia
[18]School of Medicine, University of Belgrade, Belgrade, Serbia
[19]Society of Nephrology and Dialysis of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina
[20]Department of Nephrology, Holbaek Hospital, Holbaek, Denmark
[21]Department of Clinical Sciences, Lund University, Lund, Sweden
[22]Department of Endocrinology, Nephrology and Rheumatology, Skåne University Hospital, Lund, Sweden
[23]Institute of Nephrology, Waid and Triemli City Hospital, Zurich, Switzerland
[24]Department of Nephrology P, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark
[25]Department of Paediatric Nephrology, Armand-Trousseau Children's Hospital, APHP, Paris, France
[26]Pediatric Nephrology Unit, Department for Woman and Child's Health, University-Hospital of Padua, Padua, Italy
[27]Department of Pediatric Nephrology, Gazi University, Ankara, Turkey
[28]UK Renal Registry, Bristol, UK
[29]University of Bristol Medical School, Bristol, UK
[30]Division of Nephrology, Landspitali University Hospital, Reykjavik, Iceland
[31]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland
[32]Austrian Dialysis and Transplant Registry, Department of Internal Medicine IV – Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria
[33]Nefrovisie Foundation, Utrecht, The Netherlands
[34]Department of Internal Medicine, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
[35]Inherited Kidney Diseases, Nephrology Department, Fundació Puigvert, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
Correspondence to: Anneke Kramer; E-mail: a.kramer@amsterdamumc.nl
*Share first authorship.

ABSTRACT

Background. Inherited kidney diseases (IKDs) and congenital anomalies of the kidney and urinary tract (CAKUT) are causes of kidney failure requiring kidney replacement therapy (KRT) that major renal registries usually amalgamate into the primary renal disease

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(PRD) category 'miscellaneous' or in the glomerulonephritis or pyelonephritis categories. This makes IKDs invisible (except for polycystic kidney disease) and may negatively influence the use of genetic testing, which may identify a cause for IKDs and some CAKUT.

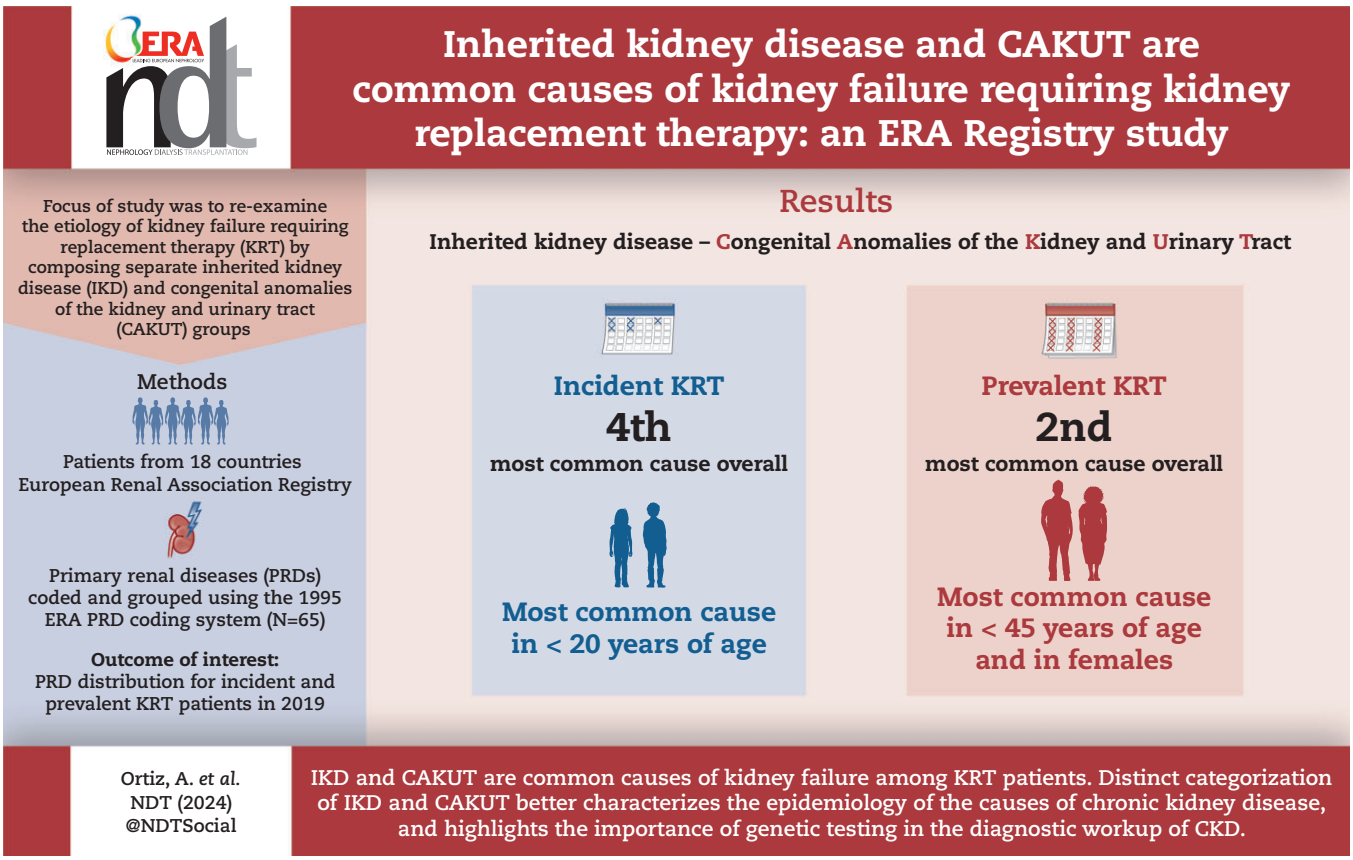
Methods. We re-examined the aetiology of KRT by composing a separate IKD and CAKUT PRD group using data from the European Renal Association (ERA) Registry.

Results. In 2019, IKD-CAKUT was the fourth most common cause of kidney failure among incident KRT patients, accounting for 8.9% of cases [IKD 7.4% (including 5.0% autosomal dominant polycystic kidney disease), CAKUT 1.5%], behind diabetes (23.0%), hypertension (14.4%) and glomerulonephritis (10.6%). IKD-CAKUT was the most common cause of kidney failure among patients <20 years of age (41.0% of cases), but their incidence rate was highest among those ages 45–74 years (22.5 per million age-related population). Among prevalent KRT patients, IKD-CAKUT (18.5%) and glomerulonephritis (18.7%) were the two most common causes of kidney failure overall, while IKD-CAKUT was the most common cause in women (21.6%) and in patients <45 years of age (29.1%).

Conclusion. IKD and CAKUT are common causes of kidney failure among KRT patients. Distinct categorization of IKD and CAKUT better characterizes the epidemiology of the causes of chronic kidney disease (CKD) and highlights the importance of genetic testing in the diagnostic workup of CKD.

Keywords: CAKUT, epidemiology, aetiology, genetic kidney disease, inherited kidney disease, kidney failure, kidney replacement therapy

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Major registries of patients on kidney replacement therapy (KRT) only report the epidemiology of a single inherited kidney disease (IKD), i.e. autosomal dominant polycystic kidney disease, which is usually diagnosed by imaging.
- This underestimates the percentage of patients with a known genetic disease causing chronic kidney disease (CKD) and underscores the importance of genetic studies to establish the cause of CKD.
- In this regard, the miscellaneous causal category represents 20% of incident KRT cases <65 years of age and 40% of childhood KRT, suggesting that current reporting methods are missing key causal information.

This study adds:

- IKD and congenital anomalies of the kidney and urinary tract (CAKUT) combined was the fourth most common cause of kidney failure among incident KRT patients, accounting for 8.9% of cases (IKD 7.4%, CAKUT 1.5%), behind diabetes (23.0%), hypertension (14.4%) and glomerulonephritis (10.6%).
- IKD-CAKUT was the most common cause of kidney failure among incident KRT patients <20 years of age (41.0% of cases).
- Among prevalent KRT patients, IKD and CAKUT combined (18.5%) and glomerulonephritis (18.7%) were the two most common causes of kidney failure overall, while IKD-CAKUT was the most common cause in women (21.6%).

Potential impact:

- Major registries of patients on KRT should individually report the IKD and CAKUT categories to provide a more granular view of the causes of CKD for different age ranges and genders.
- This approach will quantify the contribution of IKDs and CAKUT to the burden of CKD and promote the use of genetic testing to diagnose the definitive cause.
- Overall, this will contribute to the expansion of precision nephrology, by allowing a more precise causal diagnosis and facilitating the development of cause-specific therapeutic interventions.

INTRODUCTION

Since 1964, the European Renal Association (ERA) Registry has reported the main causes of kidney failure of patients receiving kidney replacement therapy (KRT) grouped into six broad categories: glomerulonephritis, pyelonephritis (i.e. chronic tubulointerstitial disease), polycystic kidney disease (PKD), diabetes, hypertension, vascular, miscellaneous and 'unknown' [1, 2], similar to other major registries, like the United States Renal Data System (USRDS; diabetes, hypertension, glomerulonephritis, cystic kidney, other urologic and other/unknown [3]). However, these categories were adopted at a time when some causes of kidney failure that are currently thought to be common had not been identified. As examples where genetic testing made an important contribution to disease awareness, *APOL1*-associated chronic kidney disease (CKD) in African Americans with so-called hypertensive nephropathy was described in 2010 and congenital anomalies of the kidney and urinary tract (CAKUT) caused by angiotensin type 2 receptor (*AGTR2*) gene defects in 1999, followed by the description of other CAKUT genes, whereas work based on exome sequencing data suggested that Alport syndrome was almost as common as PKD in 2021 [4–10]. However, genetic studies for isolated CAKUT are frequently negative, since there are other causes for CAKUT, as exemplified by the teratogenicity of renin–angiotensin system blockers. In CAKUT patients presenting a syndromic form with two or more extrarenal manifestations, the gene detection rate was found to be up to 50% [8–11].

The choice of categories to report major causes of CKD by registries may have a broad impact on the visibility of specific diseases. For example, registry-reported causes of kidney failure are repeated in textbooks and journal articles and may influence decisions regarding planning of healthcare resources, research funding and even individual physician's decisions regarding the selection of diagnostic tests and assignment of diagnoses based on a priori prevalence expectations. In this regard, it is likely that patients are diagnosed with the most common conditions aligned with the clinical features, as is frequently done for diabetic or hypertensive kidney disease. The current major causal categories could be identified using diagnostic tests available in the 20th century, such as kidney biopsy (e.g. glomerulonephritis) and imaging (e.g. PKD). At that time, there was no need for genetic testing to diagnose the major causes of CKD. As a result, the inherited kidney diseases (IKDs), with the exception of PKD as the only genetic kidney disease that has historically been reported individually, were amalgamated with CAKUT under miscellaneous, pyelonephritis and other causes. This system should now be considered as inadequate, as evidenced by the high share of 'miscellaneous' disease: 20% of incident KRT cases in those <65 years of age [just behind diabetes (21%)] and 40% of childhood KRT [2], suggesting that causal information is being underreported for a large percentage of patients. In this regard, a preliminary analysis of the Madrid [Registro Electrónico de Méritos del Servicio Madrileño de Salud (REMER)] and Catalan KRT registries found that IKD was the third to fourth most common cause of kidney failure requiring KRT [12].

In 2012, a new ERA primary renal disease (PRD) coding system was launched [13, 14], which after the update in 2018 [15], contained 281 items, expanding the 1995 ERA PRD coding system, which contained 65 items, allowing a more granular reporting of genetic diseases. Due to this new coding system, most IKDs and CAKUT can be classified as 'familial/hereditary nephropathies'. However, as this new ERA coding system has not yet been adopted by all renal registries in Europe, the ERA Registry still reports the old categories. Moreover, also in this 2012 ERA PRD coding system, many IKDs are still categorized as glomerular disease, tubulointerstitial disease or other systemic diseases affecting the kidney.

We explored the contribution of a novel category of IKD and CAKUT to the epidemiology of KRT in the ERA Registry. This new category will increase awareness among clinicians of the causal information that could be gained when using genetic testing and of the contribution of genetic disease to kidney failure.

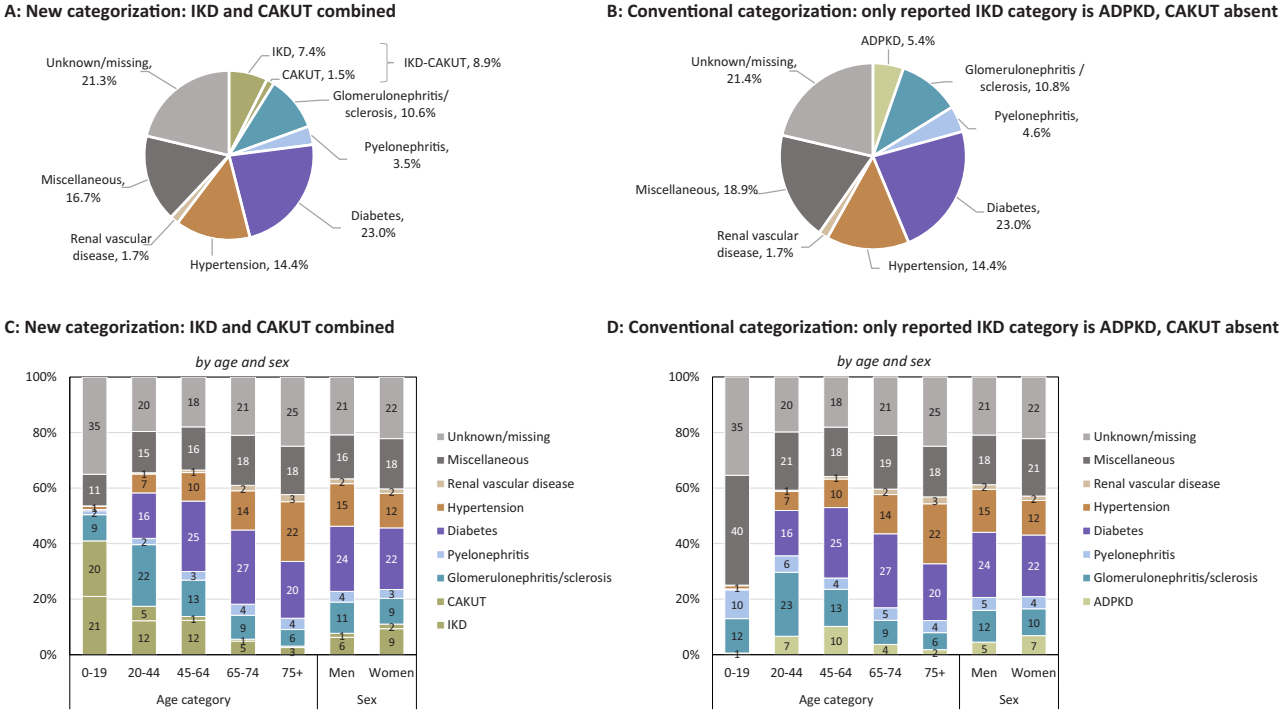


Figure 1: Distribution of PRDs of incident patients starting KRT in 2019 using the new and conventional categorization. **(A)** New categorization with IKD and CAKUT as single categories. **(B)** Categories as in ERA Registry reports from 1998 to 2019. **(C)** New categorization by age and sex with IKD and CAKUT as single categories. **(D)** Categories by age and sex as in ERA Registry reports from 1998 to 2019.

MATERIALS AND METHODS

Patient population

The ERA Registry annually collects individual data on patients with kidney failure treated with KRT via national and regional KRT registries across Europe [2] (Supplementary Methods). In the current analyses we focused on patients starting and receiving KRT in 2019. For the time trend analyses, we included patients from the years 2010 to 2019.

Primary renal disease groups

The 2012 ERA PRD codes were not available from all participating countries, nor for all years in the study period. Therefore, 1995 ERA PRD codes were used for the primary analyses, while the 2012 ERA PRD codes were only used to indicate the PRD distribution for IKD patients for which the 2012 ERA PRD codes were known. The classification of PRDs into groups applied in this study and as used in the ERA Registry annual reports is presented in Supplementary Tables S1 and S2. The cause was labelled as unknown when regional or national registries left the PRD blank ('missing') or chose 'unknown' as the cause.

Incidence and prevalence analyses

The incidence of KRT was defined as the number of patients starting KRT (dialysis or pre-emptive kidney transplantation) during a year and the prevalence was the number of patients who were alive and on KRT on 31 December. The incidence and prevalence were calculated per million of the mid-year general population (pmp) or per million age-related population (pmarp) for the analyses by age group. The adjusted incidence and prevalence were calculated by standardizing the rates to the age and sex distribution of the European Union 28-nation population in 2015 [16].

Time trend analyses

Joinpoint regression analysis [17] was used to determine time trends in the incidence and prevalence and to find points in time where a trend statistically significantly changed [18]. Time trends are expressed as annual percentage change (APC), indicating the estimated change as a percentage relative to the rate of the previous year. A two-tailed *P*-value <.05 was considered statistically significant. For the analyses using the 1995 ERA PRD codes, trend analyses focused on the years 2010–2019. For the analyses of specific IKDs, trend analyses focused on 2015–2019 (Supplementary Methods).

RESULTS

IKD and CAKUT combined was the fourth most common cause of incident KRT

In 2019, 42 972 patients started KRT in the participating countries, comprising a general population of 292.8 million, resulting in an incidence of 146.8 pmp. Of these patients, 3180 (10.9 pmp, 7.4%) had kidney failure caused by IKD and 645 (2.2 pmp, 1.5%) due to CAKUT, yielding a combined incidence of 3825 (13.1 pmp, 8.9%) (Supplementary Table S3), which made IKD and CAKUT combined the fourth most common cause of kidney failure after diabetes mellitus (23.0%), hypertension (14.4%) and glomerulonephritis (10.6%) (Fig. 1A). The incidence of IKD-CAKUT was 65% higher than for autosomal dominant polycystic kidney disease (ADPKD), the only IKD represented among conventional aetiologic categories (Fig. 1B).

Large differences existed between countries. Crude incidence rates of KRT for IKD ranged from 5.6 pmp (Serbia) to 16.5 pmp (Belgium) and CAKUT rates ranged from 0.0 pmp (Iceland) to 3.4 pmp (Bosnia and Herzegovina) (Supplementary Table S3,

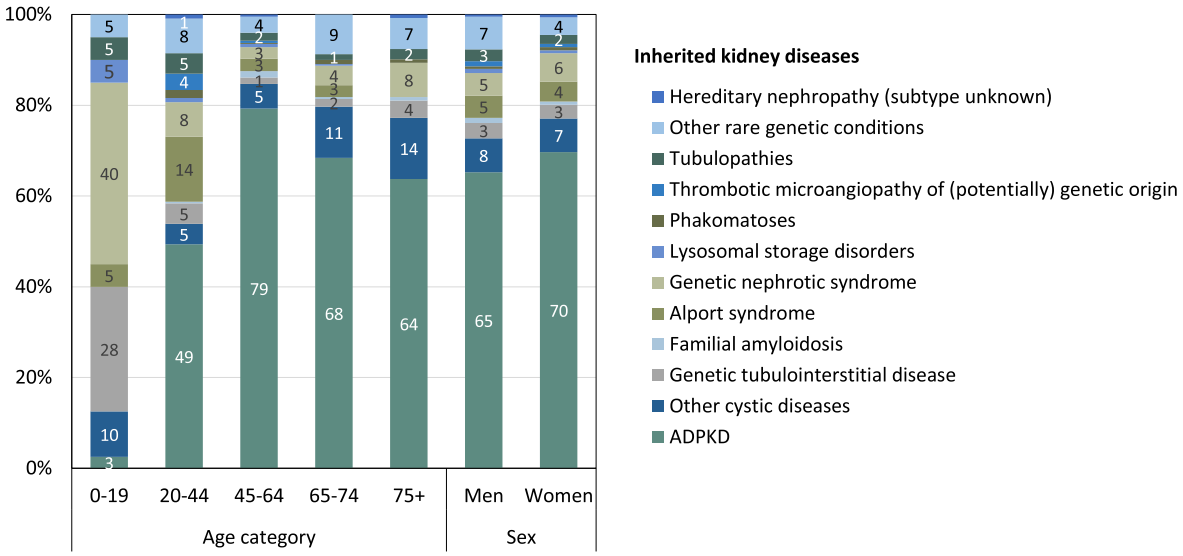


Figure 2: Distribution of the specific IKD subgroups of incident patients starting KRT in 2019, by age and sex. Using data from the subset of registries with 2012 ERA PRD data available. Data shown as a percentage of all cases of IKDs.

Supplementary Fig. S1). After adjustment for age and sex, differences between countries remained similar to the crude rates for IKD-CAKUT (Supplementary Table S4, Supplementary Fig. S2). Some of the highest incidence rates of KRT for IKD-CAKUT corresponded to countries with the highest overall KRT incidence, such as Belgium (18.0 pmp), which had almost twice the incidence of The Netherlands (10.1 pmp).

IKD and CAKUT combined were the most common cause of incident KRT in patients <20 years of age, but the incidence rate peaked at 45–74 years

In 2019, IKD-CAKUT was the most common cause of kidney failure among patients <20 years of age, accounting for 41.0% (21.0% IKD and 20.0% CAKUT) of incident KRT in this age group. For the age group 20–64 years, IKD-CAKUT was the second most common cause of kidney failure in those starting KRT; after glomerulonephritis/sclerosis (20–44 years) and diabetes (45–64 years) (Fig. 1C). Fig. 1D shows conventional ERA Registry PRD categories.

Although other causes of kidney failure were more common among persons aged 45–64 and 65–74 years, the crude KRT incidence rate of IKD-CAKUT was higher (22.6 and 22.3 pmarp, respectively) than in younger age categories (Supplementary Table S3). For IKD, the incidence rate ranged from 1.5 pmarp (<20 years) to 20.4 pmarp (45–64 years) and for CAKUT from 1.4 pmarp (<20 years) to 2.7 pmarp (65–74 years) (Table S3). In age- and sex-adjusted terms, persons aged 45–64 years (22.5 pmarp) had the highest KRT incidence rate of IKD-CAKUT (Supplementary Table S4).

IKD and CAKUT combined contributed more to the incidence of KRT in women than in men

In 2019, the incidence rate of KRT due to IKD-CAKUT was higher for men than for women: 14.8 versus 11.4 pmp (Supplementary Table S3). This was the case for both IKD (12.1 pmp versus 9.7 pmp) and CAKUT (2.7 pmp versus 1.7 pmp) (Supplementary Fig. S1) and did not change after adjustment for age (Supplementary Table S4, Supplementary Fig. S2).

The overall incidence of KRT was also higher for men. In this regard, a higher proportion of women than men started KRT because of IKD-CAKUT: 11.0% versus 7.7% (Supplementary Table S3). This was mainly due to a 49% higher proportion of women (9.4%) than men (6.3%) with IKD, while there was no difference for CAKUT (1.6% and 1.4%, respectively) (Fig. 1C). ADPKD represented a higher percentage of IKDs in women than in men (70% versus 65%) (Fig. 2). Thus, while the incidence of IKD-CAKUT was higher in men than in women, percentage-wise IKD contributed more to the overall incidence of KRT in women.

Specific IKD and CAKUT causes of incident KRT

In 2019, in the subset of registries with specific PRD data available, the overall incidence of IKD among patients starting KRT was 12.9 pmp. ADPKD was the most common IKD [8.7 pmp (67.3% of all IKD patients)], followed by other cystic diseases [1.0 pmp (7.4%)] (Table 1). However, there were differences according to age. In persons <20 years of age, the most common IKD was genetic nephrotic syndrome (40% of IKDs), followed by genetic tubulointerstitial disease (28%) (Supplementary Table S5, Fig. 2). In contrast, in patients >20 years of age, ADPKD was the most common IKD, followed by Alport syndrome. Of interest, at >75 years of age, genetic nephrotic syndrome accounted for 8% of individuals starting KRT and hereditary nephropathy subtype unknown accounted for 1% of IKD.

The most common CAKUT as a cause of kidney failure in incident KRT was sporadic primary reflux nephropathy (0.8 pmp), followed by congenital dysplasia/hypoplasia (0.5 pmp) (Table 1).

IKD and CAKUT combined was the most common cause of prevalent KRT in women

On 31 December 2019, the overall crude prevalence of KRT was 1178.2 pmp, of which 156.2 pmp (13.3% of KRT patients) was due to IKD and 61.2 pmp (5.2%) due to CAKUT, for a combined IKD-CAKUT prevalence of 217.4 pmp (18.5%) (Fig. 3A, Supplementary Table S6). After glomerulonephritis (18.7%), IKD-CAKUT was the second most common known cause of prevalent KRT, followed by diabetes (16.4%) (Fig. 3A). This differs from the current ranking position occupied by PKD (fourth) in the

Table 1: Crude distribution of specific IKD and CAKUT subgroups in incident IKD or CAKUT patients starting KRT in 2019, using data from the subset of registries with 2012 ERA PRD data available.

Characteristics	*n*	pmp (%)
Inherited kidney diseases		
ADPKD	805	8.7 (67.3)
Other cystic diseases	89	1.0 (7.4)
Other rare genetic conditions	68	0.7 (5.7)
Genetic nephrotic syndrome	67	0.7 (5.6)
Alport syndrome	56	0.6 (4.7)
Genetic tubulointerstitial disease	38	0.4 (3.2)
Tubulopathies	28	0.3 (2.3)
Familial amyloidosis	11	0.1 (0.9)
Thrombotic microangiopathy of (potentially) genetic origin	11	0.1 (0.9)
Lysosomal storage disorders	9	0.1 (0.8)
Phakomatoses	8	0.1 (0.7)
Hereditary nephropathy (subtype unknown)	6	0.1 (0.5)
Congenital anomalies of the kidneys and urinary tract		
Kidney abnormality	58	0.6 (31.8)
Congenital dysplasia/hypoplasia	45	0.5 (24.7)
Other	13	0.1 (7.1)
Urinary tract abnormality	124	1.3 (68.0)
Primary reflux nephropathy—sporadic	78	0.8 (42.9)
Congenital neurogenic bladder	14	0.2 (7.7)
Congenital vesico-ureteric junction obstruction	11	0.1 (6.0)
Posterior urethral valves	10	0.1 (5.5)
Other	11	0.1 (5.9)

Primary renal diseases included in the IKD and CAKUT groups can be found in Supplementary Table S2.

conventional ERA Registry categories (Fig. 3B). The combined contribution of IKD-CAKUT (18.5%) was 2-fold higher than the contribution of ADPKD (9.1%), the only IKD reported in conventional registry reports (Fig. 3A, B).

The prevalence IKD-CAKUT were higher in men than in women (246.4 versus 189.7 pmp) (Supplementary Table S6). This reflects a higher prevalence for both IKD (173.6 pmp) and CAKUT (72.8 pmp) for men than for women (139.6 pmp and 50.1 pmp, respectively). However, percentage-wise, IKD-CAKUT was the most common cause of prevalent KRT in women (21.6%), while it represented 16.6% of prevalent KRT in men (Fig. 3C, Supplementary Table S6). In women, both IKD (15.9%) and CAKUT (5.7%) represented a higher percentage of prevalent KRT than in men (11.7% and 4.9%, respectively).

Percentage-wise, IKD-CAKUT was the most common cause of KRT in younger patients, accounting for 59.7% (25.8% IKD, 33.9% CAKUT) of prevalent KRT among those <20 years of age and 26.6% (12.7% IKD, 13.9% CAKUT) for those 20–44 years of age (Fig. 3C, Supplementary Table S6). For patients 45–64 years of age, IKD-CAKUT was the second most common cause of KRT (22.1%: 16.6% IKD, 5.5% CAKUT) after glomerulonephritis. Fig. 3D shows conventional ERA Registry categories.

The crude prevalence of KRT for IKD-CAKUT correlated with the overall crude prevalence of KRT in different countries ($R^2 = 0.54$, $P < .001$) (Supplementary Fig. S5). The crude prevalence of IKD ranged from 28.9 pmp (Montenegro) to 201.3 pmp (Belgium) and the percentage of KRT ranged from 6.1% (Romania) to 19.4% (Finland). For CAKUT, the prevalence ranged from 9.5 pmp (Romania) to 82.0 pmp (UK) and the percentage of KRT ranged from 0.8% (Romania) to 8.8% (Bosnia and Herzegovina) (Supplementary Table S6, Supplementary Figs. S3 and S4).

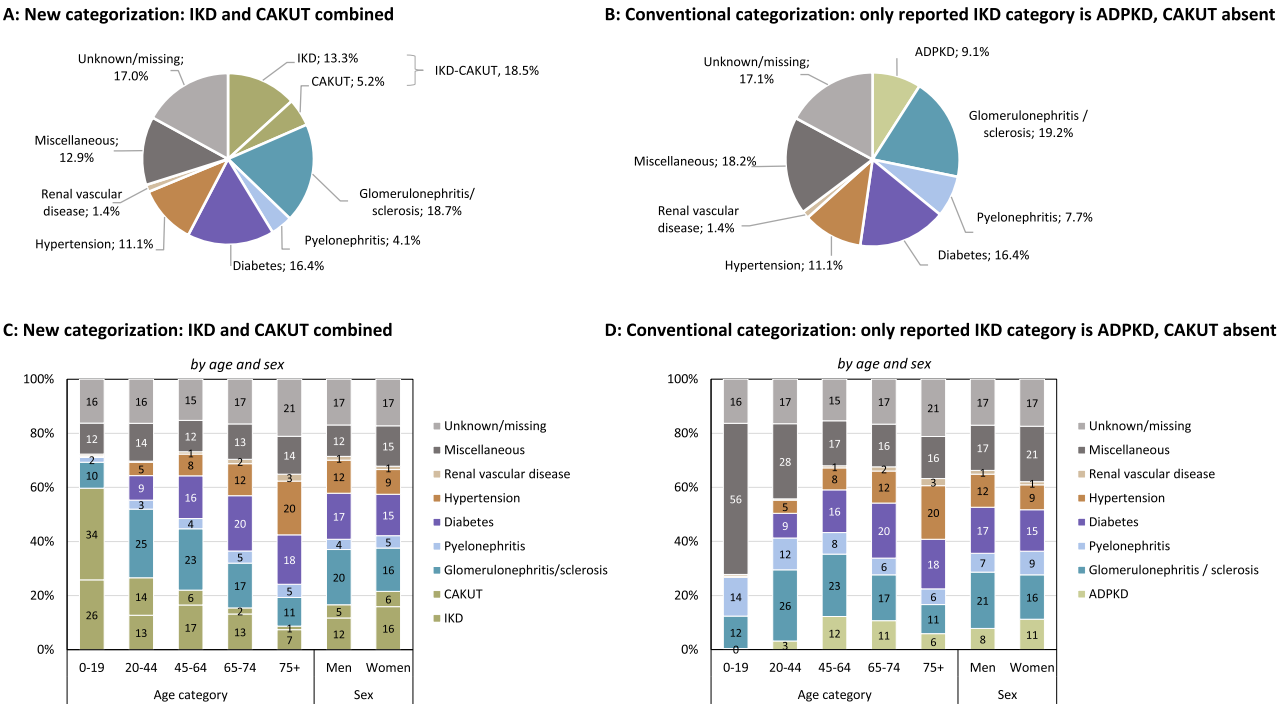


Figure 3: Distribution of PRDs of prevalent patients receiving KRT on 31 December 2019, using the new and conventional categorization. **(A)** New categorization with IKD and CAKUT as single categories. **(B)** Categories as in ERA Registry reports from 1998 to 2019. **(C)** New categorization by age and sex with IKD and CAKUT as single categories. **(D)** Categories by age and sex as in ERA Registry reports from 1998 to 2019.

Table 2: Crude distribution of specific IKD and CAKUT subgroups in prevalent IKD or CAKUT patients on KRT on 31 December 2019, using data from the subset of registries with 2012 ERA PRD data available.

Characteristics	*n*	pmp (%)
Inherited kidney diseases		
ADPKD	9503	102.8 (57.2)
Hereditary nephropathy (subtype unknown)	1772	19.2 (10.7)
Other cystic diseases	1284	13.9 (7.7)
Genetic nephrotic syndrome	1181	12.8 (7.1)
Alport syndrome	918	9.9 (5.5)
Other rare genetic conditions	668	7.2 (4.0)
Genetic tubulointerstitial disease	606	6.6 (3.6)
Thrombotic microangiopathy of (potentially) genetic origin	332	3.6 (2.0)
Tubulopathies	137	1.5 (0.8)
Lysosomal storage disorders	132	1.4 (0.8)
Phakomatoses	44	0.5 (0.3)
Familial amyloidosis	35	0.4 (0.2)
Congenital anomalies of the kidneys and urinary tract		
Kidney abnormality	1297	14.1 (24.2)
Congenital dysplasia/hypoplasia	1161	12.6 (21.7)
Other	136	1.5 (2.5)
Urinary tract abnormality	4046	43.7 (75.7)
Primary reflux nephropathy—sporadic	2781	30.1 (52.0)
Congenital vesico-ureteric junction obstruction	816	8.8 (15.3)
Congenital neurogenic bladder	272	2.9 (5.1)
Posterior urethral valves	82	0.9 (1.5)
Other	95	1.0 (1.8)

Primary renal diseases included in the IKD and CAKUT groups can be found in Supplementary Table S2.

Supplementary Table S7 shows age- and sex-adjusted prevalence data within specific countries, age groups and sex categories.

Specific IKD and CAKUT causes in prevalent KRT

In the subset of national registries with more specific PRD data available, ADPKD was the most common IKD [102.8 pmp (57.2%)], followed by hereditary nephropathy (subtype unknown) [19.2 pmp (10.7%)], other cystic diseases [13.9 pmp (7.7%)], genetic nephrotic syndrome [12.8 pmp (7.1%)] and Alport syndrome [9.9 pmp (5.5%)] (Table 2, Supplementary Table S8).

The distribution of IKDs differed according to age. In patients <20 years of age, ADPKD represented 1.8% of IKDs, and the most common IKD types were genetic nephrotic syndrome (29.6%) and genetic tubulointerstitial disease (17.6%). In patients 20–44 years of age, ADPKD was most common (20.6%), followed by Alport syndrome (16.4%) and genetic nephrotic syndrome (14.4%) (Fig. 4, Supplementary Table S8). In older patients ADPKD accounted for >60% of prevalent KRT, followed by hereditary nephropathy of unknown cause. The main difference in the distribution of IKDs between the genders was a higher percentage of ADPKD (59.3% versus 55.4% of IKDs) and a lower percentage of Alport syndrome (3.5% versus 7.2%) among women than among men.

The most common CAKUT cause of kidney failure in prevalent KRT was primary reflux nephropathy–sporadic (30.1 pmp), followed by congenital dysplasia/hypoplasia (12.6 pmp) and congenital vesico-ureteric junction obstruction (8.8 pmp) (Table 2).

Increasing incidence and prevalence of KRT for IKD but not CAKUT

Between 2010 and 2019, the crude incidence of KRT for IKD increased by 1.1% annually {APC 1.1 [95% confidence interval (CI) 0.6–1.7]} (Fig. 5A, Supplementary Table S9), from 10.4 pmp in 2010 to 11.4 pmp in 2019. The age- and sex-standardized incidence increased by 0.7% annually (95% CI 0.2–1.3) (Supplementary Table S9). The only specific IKD with increasing incidence over the last 5 years was tubulopathies [APC 21.3 (95% CI 1.6–44.9)] (Supplementary Table S10), which remained statistically significant after standardization for age and sex.

The prevalence of KRT for IKD increased from 133.1 pmp in 2010 to 168.0 pmp in 2019, i.e. by 2.9% annually between 2010 and 2015 and 2.3% annually between 2015 and 2019 (Fig. 5B, Supplementary Table S11). This increase was also observed for most specific IKDs between 2015 and 2019 (Supplementary Table S12).

For CAKUT, both the crude and standardized incidence of KRT decreased between 2010 and 2019 [APC crude incidence −2.8 (95% CI −4.0 to −1.6), APC standardized incidence −2.7 (95% CI −3.9 to −1.5)] (Fig. 5A, Supplementary Table S9). The prevalence increased by 1.0% annually until 2016 and stabilized thereafter (Fig. 5B, Supplementary Table S11).

DISCUSSION

The main finding of this study is that reporting IKD and CAKUT as a PRD category instead of reporting only PKD could better visualize the true contribution of genetic and congenital nephropathies as causes of kidney failure requiring KRT, contributing to increased awareness. IKD and CAKUT combined represent a common cause of kidney failure among incident KRT patients, and the most common cause among incident patients <20 years of age. In addition, among prevalent patients, IKD and CAKUT combined represent the second most frequent cause, and the most common cause among prevalent patients <45 years of age and in prevalent women receiving KRT. The increasing use of genetic testing is likely to uncover more IKDs among patients with CKD of unknown origin or diagnosed with hypertensive, glomerular or tubulointerstitial disease. In this regard, most African Americans with hypertensive kidney disease have *APOL1* gene variants associated with CKD progression [19]. Physicians' awareness of the burden of IKD-CAKUT will contribute to increased genetic testing and thus more precise diagnosing. This could potentially decrease the number of patients with an unknown cause of kidney disease and even of patients whose kidney disease is attributed to risk factors for CKD progression, such as hypertension, rather than to specific causes [20].

All renal registries should be encouraged to adopt the 2012 ERA PRD coding system, as this allows more precise categorization of IKD and CAKUT. Moreover, we propose to report IKD and CAKUT as individual categories—not within the 'miscellaneous', 'glomerulonephritis' or 'pyelonephritis' categories—to correctly reflect their burden and increase awareness. Despite their heterogenous clinical presentations, all IKDs are dependent on a genetic diagnosis. Defects in >600 genes are known to cause monogenic kidney diseases [21] and genetic testing may be informative in both children and adults, identifying the cause of IKDs and of some cases of CAKUT [9, 22]. Although a congenital condition differs from a genetic disorder, some IKDs are present at birth and ≈12–20% of CAKUT have a known genetic origin [23].

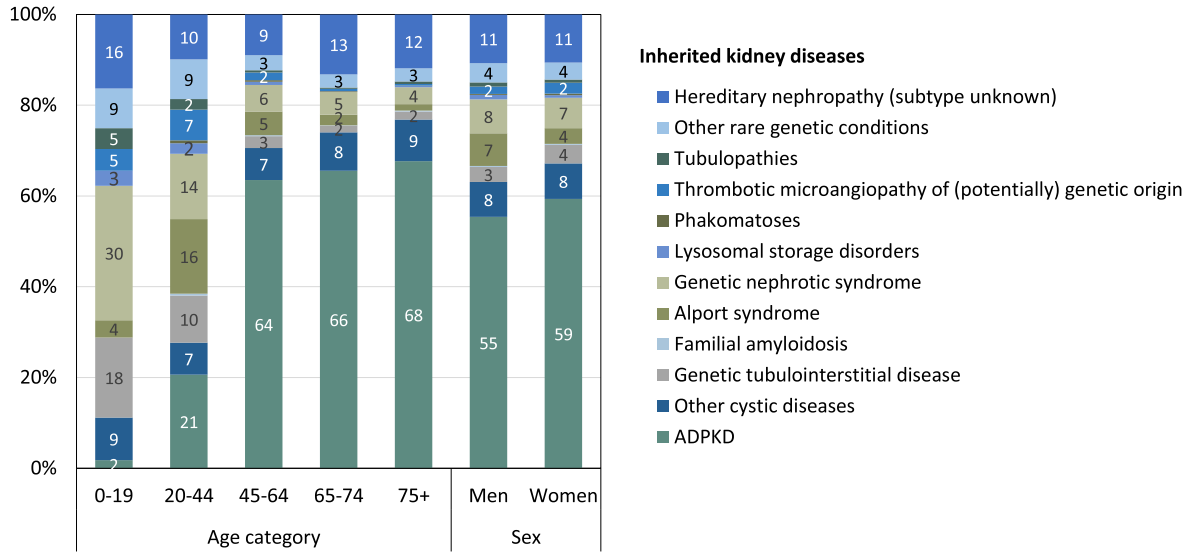


Figure 4: Distribution of the specific IKD subgroups of prevalent patients receiving KRT on 31 December 2019, by age and sex. Using data from the subset of registries with 2012 ERA PRD data available. Data shown as a percentage of all cases of IKDs.

KRT incidence and prevalence for IKD-CAKUT differed between countries, which may be influenced by year-to-year variability as well as by the variable percentage of patients with unknown and missing PRDs. Underdiagnosis due to unequal access to genetic testing and different diagnostic criteria may partially account for large divergences between countries, as well as potential pockets of local high incidence due to remote consanguinities or due to differences in ethnic diversity [24, 25]. In some areas, only confirmed genetic or imaging diagnoses may be informed as IKD while suspicions would be considered of unknown origin.

Although relatively uncommon when compared with other causes of kidney failure in the age category 45–74 years, the highest incidence rate of KRT for IKD-CAKUT was found in this age category, likely reflecting KRT for ADPKD, which peaks at 54–64 and 70–79 years for the pathogenic variants in *PKD1* and *PKD2*, respectively [25]. Other cystic diseases represented 11–14% of IKDs among persons >65 years of age. Thus IKD should also be considered as a potential cause of CKD in older adults and genetic testing should be considered. Both autosomal dominant Alport syndrome and autosomal dominant tubulointerstitial kidney disease (ADTKD) may lead to kidney failure requiring KRT in individuals >50 years of age and need genetic testing for diagnosis [26–29]. Due to the underuse of genetic testing [30], only some IKDs with a clear family history are probably labelled as IKD and the current data are expected to underestimate the burden of IKD. Underestimation may result from providing a syndrome label, such as glomerular disease for Alport syndrome, if genetic testing is not performed. Until recently, genetic testing was not considered a key item required to diagnose Alport syndrome [31, 32].

IKD-CAKUT contributed more to the burden of KRT in women than in men; roughly one in six men and one in five women on KRT had IKD-CAKUT. However, this is driven by a lower incidence or prevalence of other causes of kidney failure in women than in men. For X-linked conditions, such as X-linked Alport syndrome or Fabry disease, KRT is more common in men [29, 33], but for other IKD-CAKUT, the risk of progression to kidney failure is likely less sex dependent as compared with some major causes of kidney failure, such as diabetic kidney disease, which is more common in men.

Among IKDs, ADPKD was the most common cause of kidney failure in both incident and prevalent KRT. However, hereditary nephropathy (subtype unknown) ranked second, illustrating the underuse of genetic testing, even when a genetic cause was suspected. This deprives patients of genetic and family counselling, optimal decision-making regarding living-related kidney donation and prevention of recurrence of nephropathy in the graft. Additionally, it limits access to an increasing array of targeted therapies (e.g. tolvaptan for ADPKD, eculizumab and ravulizumab for atypical uraemic syndrome, enzyme replacement therapy and chaperones for Fabry disease and lumasiran for primary hyperoxaluria type 1) and clinical trials (e.g. inaxaplin for *APOL1* variants), while it could also result in missing extrarenal manifestations of syndromic diseases [34–40].

The incidence of patients with IKD on KRT increased between 2010 and 2019, and this was also the case for all specific IKDs between 2015 and 2019. This may represent increased use of genetic testing, as the incidence of CAKUT, usually diagnosed by imaging, decreased during this period. Additionally, the increased access for elderly ADPKD patients to KRT may have contributed [41]. Increasing prevalence may also be driven by increasing survival.

Some limitations should be acknowledged. We have grouped IKD based on codes provided to us from the respective national renal registries, although the availability of formal genetic testing is likely to be variable by country. Further work is required to determine the availability of genetic testing across Europe for patients with CKD. In the absence of clear-cut criteria to diagnose certain causes of CKD, the provided causal diagnosis may be incorrect. In some countries, a high proportion of missing or unknown diagnoses makes data unreliable, although they may also represent less access to diagnostic procedures. Kidney failure patients receiving conservative care were not represented. Additionally, kidney biopsy or genetic test results were not available and it was not known whether genetic testing had been performed. Among the strengths are the data are from a very large patient cohort assembled from multiple European national and regional KRT registries representing northern, western, and southern Europe that have provided individual patient data for many years. Extensive data quality control ensured optimal quality [2].

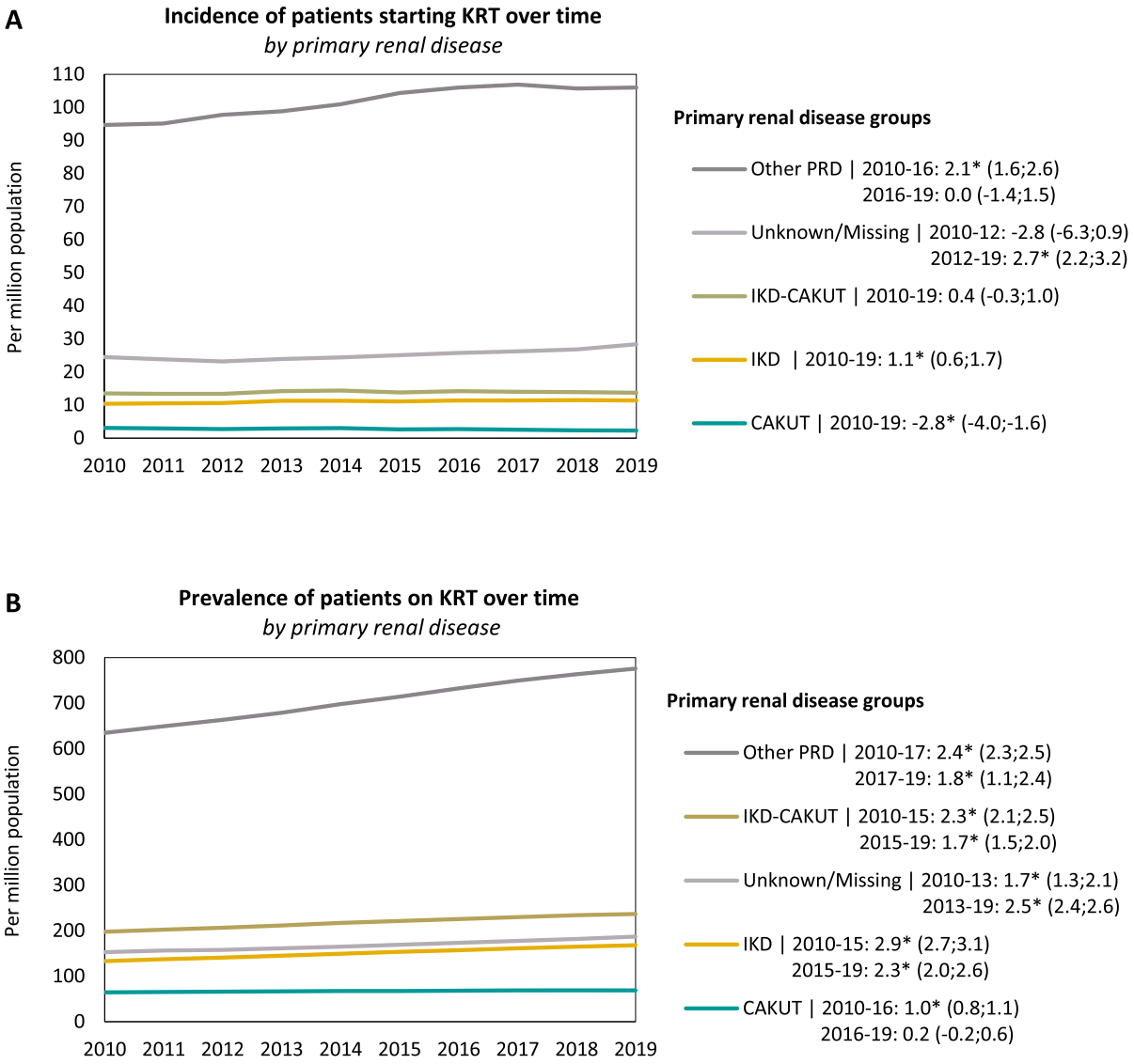


Figure 5: (A) Crude incidence and **(B)** prevalence of KRT over time between 2010 and 2019, using the new categorization of PRDs into IKD and CAKUT. Data expressed as cases per million population (pmp).

In conclusion, a new cause category encompassing IKD and CAKUT is the fourth most common cause of kidney failure in incident KRT patients, the second most common cause in prevalent KRT patients and the most common cause in young prevalent patients and in prevalent women. These findings send a strong message to health authorities, researchers and physicians regarding the need for access to genetic testing in routine clinical practice to support optimal diagnosis, counselling and treatment of patients and their families. Testing will also facilitate more granular classification of patients, which may help to enrol patients in clinical trials, avoid unnecessary immunosuppression, optimize kidney transplantation strategies, aid in family counselling in familial kidney disease and prenatal care and, in the future, prescribe targeted therapies. IKD and CAKUT should be part of the differential diagnosis of CKD at any age and presented as individual categories, outside of miscellaneous, in KRT registry reports. Initially these new categories may be reported in parallel to traditional categories to provide some continuity in data trends. The IKD category could grow as genetic testing becomes more widely available.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

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AUTHORS' CONTRIBUTIONS

A.O., A.K., V.S.S., K.J.J. and R.T. were responsible for the conceptualization, methodology and writing the original draft. A.K. was responsible for the formal analysis. G.A., O.L.R.A., A.C.G., C.S., S.T.A., P.M.F., S.M., R.S., R.N., M.A., H.R., K.H., M.S., P.M.A., S.S.S., C.P., E.V., S.A.B., L.P., R.P., J.K. and M.A.G.J.D. were responsible for review and editing. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared with any third party because the national and regional registries that provided data to the ERA Registry remain the owners of the data.

CONFLICT OF INTEREST STATEMENT

A.O. reports grants from Sanofi and consultancy/speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Idorsia, Chiesi, Otsuka, Novo Nordisk and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes. G.A. reports lecture/speaker fees from Alexion Pharmaceuticals, Recordati Rare Disease, Advicenne, Chiesi, Kyowa Kirim and Alnylam; travel support from Recordati Rare Disease, Advicenne, Chiesi and Alnylam and board membership for Alexion Pharmaceuticals, Advicenne, Dicerna, Alnylam and Novo Nordisk. P.M.F. reports royalties or licenses from UpToDate; consulting/lecture fees from Allena Pharmaceuticals, Alnylam, AstraZeneca, Bayer, Gilead, Novo Nordisk and Otsuka Pharmaceuticals and board membership for Allena Pharmaceuticals, Alnylam, AstraZeneca and Novo Nordisk. S.M. reports board membership for the Scottish Renal Registry (Public Health Scotland). R.S. reports lecture/speaker fees from AstraZeneca, Boehringer Ingelheim, Novo Nordisk and Menarini and travel support from Menarini. H.R. reports membership in the Bantao Association Board, the MKS Instruments board, the European Association of Professors Emeriti Board. M.S. reports grants from Njurfonden, SUS stiftelser och fonder and ALF (Avtal om Läkarutbildning och Forskning); consulting fees from Hansa Biopharma, Otsuka and Vifor and board membership for the Swedish Renal Registry. P.A. reports board membership for the Swiss Renal Registry and Quality Assessment Program. L.P. reports research grants from the National Institute for Health and Care Research and Academy of Medical Sciences and Kidney Research UK and support from the UK Kidney Association in the role as Paediatric Research Lead for the UK Renal Registry and a seconded role as Paediatric Research Lead of the UK Renal Registry. R.P. reports grants from the Icelandic Research Fund (Rannís) 2021–2024; travel grants from the Nordic Fabry Expert Group and board membership for the Icelandic Society of Transplantation and the Icelandic Society of Internal Medicine. K.J.J. reports board membership for the SharE RR working group of the International Society of Nephrology, all outside the submitted work. R.T. reports consultancy/speaker fees or travel support from Amicus, Sanofi-Genzyme, Kyowa Kirin, Alexion, Chiesi, Otsuka, Recordatti, Takeda, Alnylam, AstraZeneca and GSK. The remaining authors declare that they have no conflicts of interest.

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