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Systematic Scoping Review of Socioeconomic Burden and Associated Psychosocial Impact in Patients With Rare Kidney Diseases and Their Caregivers

Anna Palagyi[1], Agnivo Sengupta[1], Monica Moorthy[2], Charu Malik[2], Jonathan Barratt[3], Olivier Devuyst[4,5], Ifeoma I. Ulasi[6,7,8], Daniel P. Gale[9,10], Siyuan Wang[1], Blake Angell[1], Vivekanand Jha[2,11,12,13] and Stephen Jan[1]

[1]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia; [2]International Society of Nephrology, Brussels, Belgium; [3]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [4]Department of Physiology, Mechanisms of Inherited Kidney Disorders, University of Zurich, Zurich, Switzerland; [5]Division of Nephrology, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium; [6]Renal Unit, Department of Medicine, College of Medicine, University of Nigeria, Ituku-Ozalla, Enugu, Nigeria; [7]Renal Unit, Department of Medicine, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria; [8]Renal Unit, Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria; [9]National Registry of Rare Kidney Diseases, Bristol, UK; [10]Department of Renal Medicine, University College London, London, UK; [11]The George Institute for Global Health, University of New South Wales, New Delhi, India; [12]School of Public Health, Imperial College London, London, UK; and [13]Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, Karnataka, India

Introduction: Rare kidney diseases constitute a significant public health challenge but have attracted limited research investment. The evidence about the socioeconomic burden of rare kidney diseases has not been systematically examined. Such evidence is critical for generating the advocacy and awareness necessary to impel scientific and policy investment in targeted care in health systems worldwide. We aimed to evaluate the socioeconomic burden borne by patients with rare kidney diseases, their families, and caregivers, and the related psychosocial impact.

Methods: We undertook a systemic scoping review of the recent evidence of the socioeconomic and psychosocial burden of rare kidney diseases, to identify gaps in the understanding of this burden across contexts and factors influencing them. Three databases and the grey literature were searched for relevant studies published in the 10 years before April 30, 2023.

Results: Fifty-three articles met the inclusion criteria; one-quarter of these articles included rare disease cohorts in which the kidney was the primary organ affected, and 91% of studies were conducted in high-income countries. Evidence of substantial life-long socioeconomic burden emerged across the following 4 main categories: education ($n = 17$ articles [32%]), work and employment ($n = 40$ [75%] articles), psychosocial and emotional impact ($n = 17$ [32%]), and out-of-pocket expenses ($n = 15$ [28%]).

Conclusion: Significant gaps in our understanding of the socioeconomic burden remain, particularly in lower-resource health systems, among traditionally marginalized populations, and for rare diseases for which kidney is the primary affected organ. Further exploration of socioeconomic burden within these populations is vital to inform effectively targeted investment in advocacy and health care innovation for affected individuals.

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Rare kidney diseases affect < 1 in 2000 people individually[1]; however, they collectively constitute a significant and overlooked public health challenge. These conditions encompass a diverse range of almost 300 disorders,[2] the majority of which are genetically acquired[3,4] and start in childhood.[3] As a consequence of their individual low frequency, rare kidney diseases have attracted limited investment in the advocacy and research necessary to drive the advancement of accessible diagnostic technologies and effective

Correspondence: Anna Palagyi, The George Institute for Global Health, PO Box M201, Missenden Rd, Sydney, New South Wales 2050, Australia. E-mail: apalagyi@georgeinstitute.org.au
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pharmaceutical therapies. This has hampered the optimization of nonclinical support for patients and caregivers. Thus, individuals with suspected rare kidney diseases often experience difficult and protracted diagnostic journeys,[5,6] significant treatment uncertainty with few options,[6] a higher likelihood of kidney failure than those with kidney disease attributed to more common conditions,[7] and lifelong disability with consequential economic and societal costs.[8]

The socioeconomic burden of disease encompasses both direct and indirect costs associated with their diagnosis and treatment. Direct costs are most commonly carried by the health system, including government and nongovernment sectors, individuals, and families.[8,9] Additional indirect costs for patients and caregivers include those related to foregone education, work productivity, and impacts on psychosocial well-being.[10] Although a small but growing body of evidence highlights the socioeconomic burden of rare diseases,[8,11,12] there is little evidence that specifically examines the socioeconomic burden of rare kidney diseases and related psychosocial impacts. Such evidence is critical for generating the advocacy and awareness necessary to encourage investment in care for rare kidney diseases; optimize disease outcomes; and minimize costs for health systems, affected individuals, and caregivers.[12,13]

The United Nations has highlighted the importance of recognizing rare diseases in policies, and in December 2021 all 193 member states adopted the first United Nations Resolution on "Addressing the Challenges of Persons Living with a Rare Disease and their Families."[14] Notably, this resolution goes beyond health and affirms that addressing the needs of persons living with a rare disease is essential to advancing the 2030 Sustainable Development Agenda, which includes access to education and employment, reducing poverty, tackling gender inequality, and supporting social inclusion.[15] It is well-recognized that the support needs of people living with a rare disease, including families and caregivers, are complex.[16] Further, systemic inequalities and widespread disparities in the ability of health systems, communities, and individuals to manage these complex needs exist across populations and jurisdictions.[6] The brunt of these disparities is borne disproportionately by socioeconomically disadvantaged populations. If countries are to take effective measures to attain their commitments for those affected by rare diseases, context-tailored and disease-specific efforts are critical. Understanding how patients and their support network experience their lifelong journeys with such conditions is at the core of effective action.

As an initial step toward growing such understanding, in this review we synthesize recent evidence of the socioeconomic impact of rare kidney diseases on patients and caregivers. Based on the available literature, we identify the socioeconomic costs borne by patients, families, and caregivers; gaps in the understanding of this burden across contexts; factors influencing burden; and (where available) coping strategies to address these. Priorities for further research and policy initiatives targeted at reducing the socioeconomic burden of rare kidney diseases are also suggested.

METHODS

Review Question

The systematic scoping review[17] sought to address the following questions by identifying all relevant published evidence reporting the direct and indirect socioeconomic burden of rare kidney disease and associated psychosocial impact, for patients and their families or caregivers:

- What is the current evidence of the socioeconomic burden and psychosocial impact of rare kidney diseases in patients and caregivers (and where are the evidence gaps)?
- What is the extent of this burden in different geographic and socioeconomic contexts?
- What factors are associated with a greater risk of such a burden, including population and disease characteristics?
- What coping strategies have been initiated by patients and caregivers to address this burden?

Search Strategy

We searched the peer-reviewed (Medline, PubMed, and EMBASE electronic databases) and the grey literature for observational studies published within the 10 years before April 30, 2023, by using a combination of key words and MESH terms, including: "socioeconomic factors," "cost of illness," "health care costs," "economic burden," "household," "education," "employment," and "societal." Our search included a comprehensive list of 285 rare kidney diseases, developed by combining diseases with the Orphanet classification of "rare renal disease"[18] with those listed on the European Rare Kidney disease registry.[19] Disease terms on this combined list were then cross-checked against the Groopman list,[20] and a brief review of the literature was undertaken to confirm that there was a reported kidney disease association for all diseases on the list. The disease was removed from the list if a reported association could not be found.

Table 1. Selection criteria

Inclusion	• Reported data on socioeconomic burden or psychosocial impacts of a rare kidney disease, as defined by either direct or indirect costs to patients and their family or caregivers relating to the following: (i) access to care, (ii) education, (iii) income, (iv) employment, and (v) social support. • Any stage of rare kidney disease • All geographic settings (high, low-, and middle-income countries; any population group) • Observational (i.e., cohort) studies, case-control studies, cross-sectional studies and qualitative studies • Published in English
Exclusion	• Socioeconomic impact as the result of a rare kidney disease • Direct or indirect costs borne by patients or their family or caregivers

The full search strategy is presented in the Supplementary Material. The literature inclusion and exclusion criteria are presented in Table 1.

Data Extraction and Synthesis

The results of searches were combined, and duplicate references were removed. Two authors (AS and AP) independently screened all titles and abstracts of studies identified by the initial search for relevance. All potentially relevant studies were retrieved as full-text articles and independently reviewed by 1 author (AS) for inclusion. The reference lists of included articles were reviewed to identify other relevant studies. Data extraction was undertaken by 1 author (AS) initially and verified by a second author (AP) against the original studies. Disagreements were resolved by consensus. Data were extracted into a purpose-built Excel spreadsheet and included the study details (publication date, study design, and years of data collection); setting (country and health care setting); study population (mean age and sex [biological, according to the definition applied by the original research] distribution, insurance status, and ethnicity); kidney disease of interest; socioeconomic burden data; and coping strategies to alleviate burden (where assessed). Data were then grouped by category of socioeconomic burden by applying the Arksey and O'Malley Framework for scoping reviews,[17] and a narrative synthesis approach[21,22] was used to summarize the key findings.

This review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews (PRISMA-ScR).[23]

RESULTS

This review identified 53 articles (48 peer-reviewed articles and 5 grey literature reports) meeting the full inclusion criteria (Figure 1). Only 5 of the included studies (9%) were conducted in low- or middle-income countries. Thirteen articles (25%) included rare disease cohorts in which the kidney was the primary organ affected; all other articles ($n = 40$; 75%) focused on rare diseases with systemic effects, including kidney complications. Thirty-four articles (64%) reported on socioeconomic burden from the patient perspective, 14 articles (26%) reported both patient and caregiver burden, and 5 articles (9%) focused on the socioeconomic burden on caregivers. The characteristics of included articles are presented in Table 2.

Socioeconomic and psychosocial factors examined included impact on work and employment ($n = 40$ articles [75%]); impact on education ($n = 17$ [32%]); psychosocial and emotional impact ($n = 17$ [32%]); and out-of-pocket expenses, including care affordability ($n = 15$ [28%]). The findings of socioeconomic burden study are presented below and summarized in Table 3.

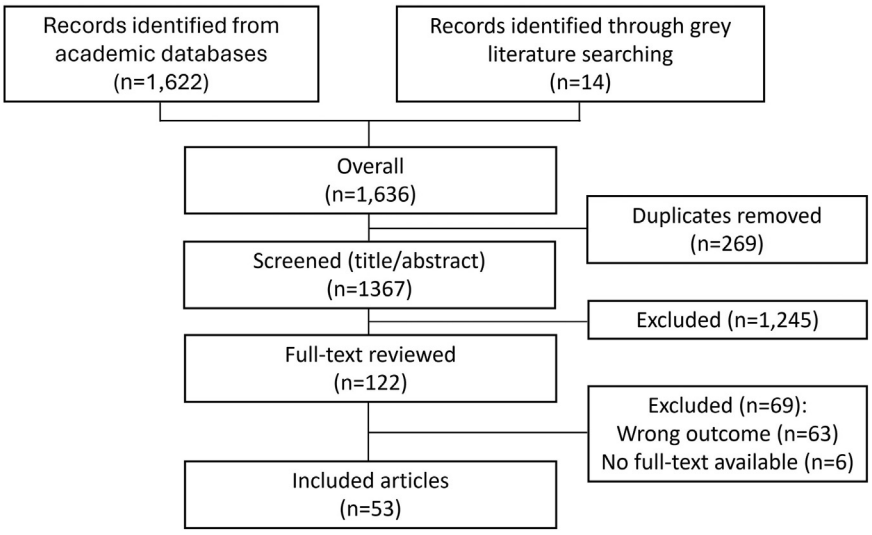

Figure 1. Flow chart of the literature selection.

Table 2. Characteristics of included studies, grouped by the type of rare kidney disease

Author	Study design	Study period	Location (country/ies)	Disease of interest	Population characteristics			Socioeconomic/psychosocial aspects explored
					Patients or caregivers (patient population)	Cohort size *n* (% female)	Age, yrs Mean (SD)	
Gouya *et al.*[24]	Prospective cohort	September 2014–November 2016	USA, Europe	Acute hepatic porphyria	Patients (adult)	112 (89.3)	SLE: 49 (1.4); non-SLE: 50 (0.7)	Economic impact
Wheeden *et al.*[25]	Qualitative	Not reported	USA, UK	Acute hepatic porphyria	Patients (adult)	14 (100)	45.4 (14.9)	Impact on work or school
Feldman *et al.*[26]	Meeting report (Qualitative)	August 2018	USA	Alport syndrome[a]	Patients (pediatric and adult) & caregivers	50 (50)	< 18: 33% 18–59: 60%	Experiences living with Alport syndrome, impact of disease symptoms on daily life, perspectives on available treatments.
Aigbogun *et al.*[27]	Cross-sectional	September 2018	USA	Autosomal dominant polycystic kidney disease[a]	Patients (adult)	300 (69.3)	52.1 (12.8)	Impact on work productivity
Cloutier *et al.*[28,a]	Comparative	2018	USA	Autosomal dominant polycystic kidney disease[a]	Patients (pediatric and adult) & caregivers	140,598 (NA)	NA	Out-of-pocket expenses, loss of productivity for employed people; productivity loss from caregiving
Eriksson *et al.*[29]	Cross-sectional	April–December 2014	Denmark, Finland, Norway, Sweden	Autosomal dominant polycystic kidney disease[a]	Patients (adult)	243 (53.9)	CKD 1–3 = 52 (13) CKD 4–5 = 57 (12) Dialysis = 64 (10) Transplant = 59 (10)	Activity and work impairment; annual disease-related costs
Oberdhan *et al.*[30]	Qualitative	Not reported	North America, Europe, Australia, Asia, and South America.	Autosomal dominant polycystic kidney disease[a]	Caregivers (pediatric and adult)	139 (66.9)	44.9 (NA)	Emotional impact, impact on work and employment; financial impact, impact on social and leisure activities
Oberdhan *et al.*[31]	Qualitative	2012–2013	13 countries (in North America, Europe, Australia, Asia, and South America)	Autosomal dominant polycystic kidney disease[a]	Patients (pediatric)	33 (42.4)	14.6 (1.8)	Impact on daily life; impact on school; social impacts
Biswas *et al.*[32]	Cross-sectional	May 2016–April 2017	India	Beta-thalassemia major	Caregivers (pediatric)	324 (75.9)	NA	Caregiver quality of life
Elzaree *et al.*[33]	Case-control	Not reported	Egypt	Beta-thalassemia major	Patients (pediatric)	100 (50.0) Cases = 50 (50) Controls = 50 (50)	Cases = 11.05 (3.8) Controls = NA	School performance; adaptive functioning
Spencer *et al.*[34]	Prospective cohort	2018–2020	India	Bladder exstrophy-epispadias complex[a]	Patients & caregivers (pediatric)	72 (19.4)	NA	Psychosocial burden on families or caregivers, psychological outcomes in caregivers of children who underwent surgery
Feldman *et al.*[35]	Meeting report (Qualitative)	August 2017	USA	C3 glomerulopathy[a]	Patients (adult) & caregivers (pediatric and adult)	5	NA	Experiences living with disease, impact of disease symptoms on daily life, perspectives on available treatments.

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Table 2. (Continued) Characteristics of included studies, grouped by the type of rare kidney disease

Author	Study design	Study period	Location (country/ies)	Disease of interest	Population characteristics			Socioeconomic/psychosocial aspects explored
					Patients or caregivers (patient population)	Cohort size *n* (% female)	Age, yrs Mean (SD)	
Randall *et al.*[36]	Qualitative	Not reported	USA	Classical galactosemia[a]	Patients & caregivers (adult)	20 Patients = 12 (41.7) Caregivers = 8 (75)	Patients = 29.3 (10.24); Caregivers = 55.9 (9.52)	Social impact, caregiver burden
Bashorum *et al.*[37]	Cross-sectional	June–September 2021	France, Germany, UK	Fabry Disease	Patients & caregivers (pediatric)	28 Patients = 14 (42.9) Caregivers = 14 (21.4)	NA	Caregiver work absenteeism
Qi *et al.*[38]	Retrospective cohort	May–June 2018	China	Gaucher disease	Patients & caregivers (pediatric and adult)	49 (49.0)	9.3 (10.69)	Indirect costs; caregiver burden
Feng *et al.*[39]	Database analysis	2012–2016	China	Hemolytic uremic syndrome[a]	Patients (adult)	1060 (450)	49.65 (15.82)	Incidence and cost of disease
Holmes *et al.*[40]	Cross-sectional	July–November 2019	UK	Immune-mediated thrombotic thrombocytopenic purpura (iTTP)	Patients (adult)	35 (97.1)	13.5 (9.44)	Impact on employment
Theodore-Oklota *et al.*[41]	Cross-sectional survey	Not reported	USA & Canada	Kabuki syndrome	Caregivers (pediatric)	57 (94.7)	Caregivers = 40 (8.8) Child = 9 (7.1)	Caregiver burden
Theodore-Oklota *et al.*[42]	Qualitative	Not reported	USA & Canada	Kabuki syndrome	Patients & caregivers (pediatric and adult)	68 Patients = 11 (NA) Caregivers = 57 (NA)	Not reported	Impact on social life and communication
Simon *et al.*[43]	Cross-sectional survey	Not reported	USA	Nephrotic syndrome[a]	Patients & caregivers (pediatric and adult)	45 (75.6)	NA	Annual direct and indirect costs
Foji *et al.*[44]	Qualitative	2019–2020	Iran	Neurofibromatosis type 1	Patients (adult)	18 (55.6)	NA	Failing and falling behind in life, impact on social life
Yang *et al.*[45]	Cross-sectional	December 2020–January 2021	USA	Neurofibromatosis type 1	Caregivers (pediatric)	95 (88.4)	Not reported	Caregiver burden, work productivity and impairment
Michaeli *et al.*[46]	Retrospective cohort and costing	2000, 2010, 2020	Germany	Renal cell carcinoma[a]	Patients (pediatric and adult)	NA	NA	Societal perspective
Dattani *et al.*[47]	Cross-sectional study	September 2016–March 2017	North America, British Isles, Europe, Australasia, Asia and South America	Retroperitoneal fibrosis[a]	Patients (adult)	229	51 (range: 17–76 yrs)	Psychological burden, perceptions of care
Schwartz *et al.*[48]	Cross-sectional	Not reported	USA	Robinow syndrome	Patients (pediatric and adult)	13 (23.1)	Children = 10.2 (NA); Adults = 35.4 (NA)	Attention and executive functioning; learning, school, and job functioning; income from employment
Rice *et al.*[49]	Database Analysis	January 1998–March 2015	USA	Sarcoidosis	Patients (adult)	Cases=7119 (58.5) Controls = 7119 (57.0)	50.3 (10.4)	Disability and medical-related absenteeism during the outcome period
Sikjær *et al.*[50]	Database Analysis	1998–2010	Denmark	Sarcoidosis	Patients (pediatric and adult)	Cases = 9119 (47.4) Controls = 36,432 (47.4)	NA	Healthcare costs for patients before and after diagnosis
Fetuga *et al.*[51]	Cross-sectional	Not reported	Nigeria	Sickle cell disease	Caregivers (pediatric)	216 (90.7)	37.7 (7.8)	Caregiver burden; school absenteeism

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Table 2. (Continued) Characteristics of included studies, grouped by the type of rare kidney disease

Author	Study design	Study period	Location (country/ies)	Disease of interest	Population characteristics			Socioeconomic/psychosocial aspects explored
					Patients or caregivers (patient population)	Cohort size *n* (% female)	Age, yrs Mean (SD)	
Abu Bakar *et al.*[52]	Cross-sectional	March–July 2017	Malaysia	Systemic lupus erythematosus	Patients (adult)	167 (87.4)	38.2 (9.8)	Employment
Booth *et al.*[53]	Cross-sectional (Qualitative)	September–October 2017	UK	Systemic lupus erythematosus	Patients (adult)	393 (97.2)	NA	Impact on work and employment
Booth *et al.*[54]	Qualitative	September–October 2017	UK	Systemic lupus erythematosus	Patients (adult)	72 (100)	NA	Impact on employment and work-related environment
Ekblom-Kullberg *et al.*[55]	Case-control	Not reported	Finland	Systemic lupus erythematosus	Patients (adult)	181 (100)	44.0 (11.9)	Employment and absenteeism; work disability
Garris *et al.*[56]	Prospective cohort	December 2010–August 2011	USA	Systemic lupus erythematosus	Patients (adult)	846 Cases = 546 (96.5) Controls = 300 (96)	38	Work productivity
Grabich, S. *et al.*[57]	Retrospective cohort	2016–2018	USA	Systemic lupus erythematosus	Patients (adult)	Cases = 473,099 (90.8) Controls = 2,524,667 (94.4)	9.8 (5.3)	Impact on work and employment, access to care
Groot *et al.*[58]	Retrospective cohort	November 2013–April 2016	Nigeria	Systemic lupus erythematosus	Patients (adult)	106 (92.5)		Impact on education and employment
Kent *et al.*[59]	Cross-sectional	November 2014–February 2015	UK	Systemic lupus erythematosus	Patients & caregivers (adult)	Patients = 121 (77.7) Caregivers = 31 (48.0)	40	Work and income, impact on carers, misdiagnosis and treatment delays
McCormick *et al.*[60]	Cross-sectional survey	1996–2010	Canada	Systemic lupus erythematosus Systemic sclerosis	Patients (adult)	SLE = 167 (94.0) SSc = 42 (88.1)	SLE = 54.6 (13.1) SSc = 59.5 (12.0)	Impact on work productivity, average weekly costs for time lost per person from paid work
Narayanan *et al.*[61]	Retrospective observational	July 2004–December 2009	USA	Systemic lupus erythematosus	Patients (adult)	Cases = 13,460 (91.6) Controls = 13,460 (88.9)	SLE = 45.6 (10.9); Controls = 47.1 (11.4)	Work loss; adjusted indirect costs
Pisoni *et al.*[62]	Observational cross-sectional	Not reported	Argentina	Systemic lupus erythematosus	Patients (adult)	419 (89.3)	38.7 (12.9)	Work disability
Williams *et al.*[63]	Qualitative	January–June 2012	USA	Systemic lupus erythematosus	Patients (adult)	10 (100)	47.6	Patient experiences related to travel and travel-related burden
Castellví *et al.*[64]	Cross-sectional	September 2012–January 2013	Spain	Systemic sclerosis	Patients (adult)	199 (82.4)	54	Work productivity; employment status
Knarborg *et al.*[65]	Retrospective cohort	2002–2015	Denmark	Systemic sclerosis	Patients (adult)	Cases = 1869 (75.5) Controls = 7496 (75.5)	NA	Annual average direct and indirect costs
Lopez-Bastida *et al.*[66]	Retrospective cross-sectional	September 2011–February 2012	Spain	Systemic sclerosis	Patients (adult)	147 (85)	38	Direct healthcare and nonhealthcare costs; relation between costs and disability levels; cost differences based on disease duration

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Table 2. (Continued) Characteristics of included studies, grouped by the type of rare kidney disease

Author	Study design	Study period	Location (country/ies)	Disease of interest	Population characteristics			Socioeconomic/psychosocial aspects explored
					Patients or caregivers (patient population)	Cohort size *n* (% female)	Age, yrs Mean (SD)	
Padala *et al.*[67]	Retrospective cross-sectional	2005–2019	New Zealand	Systemic sclerosis	Patients (adult)	86 (90.8)	NA	Work limitations; direct costs
Xiang *et al.*[68]	Prospective cohort	October 2017–January 2020	Singapore	Systemic sclerosis	Patients (adult)	111 (87.4)	49.4 (10.5)	Unemployment; work productivity loss; activity impairment; economic burden of unemployment and work productivity
Tedone *et al.*[69]	Cross-sectional survey	Not reported	Italy	Transfusion-dependent Beta-Thalassemia	Patients (pediatric and adult)	105 (54.3)	42.4 (9.16)	Impact on work and employment
Biederman[70]	Mixed-methods survey	July–November 2018	USA	Tuberous sclerosis complex	Patients (adult)	175	Range: 18–45 yrs	Reproductive decisions
Grau *et al.*[71]	Retrospective cohort	2019	Germany	Tuberous sclerosis complex	Patients & caregivers (pediatric)	Patients = 184 (48.4)	33	Total direct costs, nursing and other informal care costs, productivity loss from caregiving, drivers of cost
Jansen *et al.*[72]	Registry-based cohort	2017	UK	Tuberous sclerosis complex	Patients & caregivers (pediatric and adult)	143 (61.5)	NA	Impact on career/education progress, access to care; caregiver-reported burden
Skalicky *et al.*[73]	Cross-sectional survey	May–June 2012	USA	Tuberous sclerosis complex	Patients & caregivers (pediatric and adult)	609 (59.9)	37.7 (10.8)	Direct cost burden; work productivity
Barra *et al.*[74]	Cross-sectional	June–December 2015	USA	Vasculitis	Patients (adult)	421 (69.6)	53 (13)	Work disability; work productivity
Lo *et al.*[75]	Qualitative	2019	United Kingdom, Finland, France, Luxembourg and Germany	X-linked hypophosphatemia	Patients (adult)	30 (70.0)	45 (14.1)	Psychosocial impact
Mosheva *et al.*[76]	Cross-sectional	2017	Israel	22q11.2 deletion syndrome	Patients (pediatric and adult)	260 (48.5)	21.3 (10.8)	Impact on education

CKD, chronic kidney disease; NA, not available; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UK, United Kingdom; USA, United States of America.
[a]Denotes rare kidney diseases in which the kidney is the primary organ affected.

Table 3. Summary of the socioeconomic impacts of rare kidney diseases

Socioeconomic or psychosocial factor	Areas of impact
Work and employment	• Loss of productivity or work absenteeism because of disease-related disability (patients)[24–29,40,44,49,52–58,60,61,64,67–70,72–74,77] • Loss of productivity or work absenteeism because of caregiving responsibilities (caregivers)[30,37,41,45,59,71–73] • Early job discontinuation (patients)[54,66,74] • Reduced career advancement because of disease progression (patients)[53,54,72]
Education	• School absenteeism (patients)[26,31,35,43,51,58,70,73] • Interrupted or delayed education (patients)[25,58,72,76] • Impairment of school performance (patients).[25,36,48,73]
Psychosocial and emotional impact	• Anxiety and depression[25,26,30,31,34–36,42,44,48,51,53,54,59,62,70,72] - Caregiving responsibilities (caregivers)[30,35,51] - Patients' loss of employment (patients)[44,53,54] - Financial stress because of loss of employment (patients and caregivers)[51,54] - Parental concerns about child's future fertility and marital prospects (caregivers)[34] • Inability to engage in social activities (patients and caregivers)[30,59] • Parental guilt about genetically linked disease (caregivers)[26,27,30,70,75]
Out-of-pocket expenses and care affordability	• Health care copayments (patients and caregivers)[35,43,71,74] • Medications or diagnostics (patients)[43] • Ancillary medical devices (patients)[26] • Transport costs (patients and caregivers)[63,71] • Diet-related costs (patients)[43] • Financial constraints leading to care unaffordability (patients and caregivers)[25,26,30,32,35,43,51,54,63,70,74]

Impact on Work and Employment

Disease-related disability burden for patients and caregiving responsibilities for caregivers were the most commonly reported causes of productivity loss and work absenteeism.[26,45,49,58,61,68,70] An assessment of direct non-healthcare costs and labor productivity losses in 147 patients with systemic sclerosis (SSc) in Spain found that mean lost productivity costs were €7302 per person, of which early retirement accounted for 80.7% of costs, and sick leave accounted for 19.3%.[66] A study that evaluated the economic burden of autosomal dominant polycystic kidney disease (ADPKD) in 140,598 patients in the United States estimated the annual indirect costs at $1.4 billion.[28] Among these costs, 35% were associated with increased unemployment and reduced work productivity among individuals with end-stage renal disease (ESRD) receiving kidney replacement therapy.[28] Overall indirect costs stemming from the loss of productivity at work were estimated to be about $390 million, with almost two-thirds of these costs incurred by those in the early stages of disease.[28] Additional work-related indirect costs included missed opportunities because of early job discontinuation and reduced career advancement because of disease progression.[25,43,53,72] Financial difficulties were commonly noted, primarily resulting from income reduction.[32,54,74]

Population-based estimates of lost productivity costs in 671 Canadians with systemic lupus erythematosus (SLE) and SSc reported that those with SLE or SSc would incur an additional CAD$4494 ($3318) and CAD$3582 ($2644), respectively, in lost productivity costs each year compared with the costs for an individual without these diagnoses.[60] We found that patients with SLE and SSc had 2.4 times and 2.6 times greater odds, respectively, of being unemployed because of their health than individuals without these diseases.[60] Similar findings were reported by an observational study of over 13,000 patients with SLE in the United States, where those with SLE had up to 2 times more hours of absence from work or short-term disability and twice the amount of total indirect costs than their matched controls.[61]

Caregivers of children also faced financial burden because of lost income stemming from caregiving responsibilities.[71] In a study of 216 caregivers (in which 189 of 216 [87.5%]were mothers) of patients with sickle cell anemia in Nigeria, 91% respondents reported that they had lost income or financial benefits because of the time spent caring for their child.[51] Among 184 caregivers (in which 89 of 184 [48%] were females) of children and adolescents with tuberous sclerosis complex in Germany, 111 (60%) reported having changed their working situation or remaining out of work because of caregiving responsibilities, with a total mean indirect cost of €3184 ($3843).[71] Mothers reported quitting work and reducing working hours more than fathers (13% vs. 1% and 27% vs. 4%, respectively), and experienced over 12-fold greater mean lost productivity costs than fathers in a 3-month period.[71]

Five articles reported impairment in daily activities because of disease progression, which was measured as differences in work impairment or productivity between various disease strata.[27–30] A retrospective study that estimated direct and indirect costs of ADPKD in 243 patients in 4 Nordic countries reported that activity impairment was highest (53%) among patients on dialysis but also substantial (30%) in both patients with late-stage chronic kidney disease and among

transplant recipients.[29] In addition, work impairment was highest among dialysis patients (42%), followed by chronic kidney disease stages 4 and 5 (23%), transplant recipients (16%), and chronic kidney disease stages 1 to 3 (9%).[29]

Impact on Education

Four of 15 articles that assessed the impact of rare kidney diseases on education reported school absenteeism because of illness.[26,51,58,73] A qualitative study involving 33 adolescents with ADPKD from 13 countries spanning Asia, Europe, South America, North America, and Australia found that over 18% of participants had missed school at some point in time because of the disease.[31] Some participants also reported feeling uncomfortable while attending school because of the need to urinate frequently.[31] A study of socioeconomic burden in 106 adults (92% female) in Nigeria with childhood-onset SLE found that 91% of participants reported their education to have been impacted by the disease, including school absenteeism (69% participants), being held back by a year (29%), and dropping to lower level of education (22%).[58]

In a European study of 143 patients and caregivers affected by tuberous sclerosis complex, 17% of participants reported either their education or career progression being impacted.[72] Moreover, 37.5% stated that the disease had impaired their ability to attain their desired education level.[72]

Academic and occupational trajectories from childhood to adulthood of patients with 22q11.2 deletion syndrome (22q11.2DS), were reported in a study of 260 affected individuals from Europe and Israel.[76] Findings highlighted that though cognitive abilities played a key role in determining whether children or adolescents would enter mainstream education, adaptive functioning became a more reliable indicator for employment as individuals with 22q11.2DS grew older. Although most children with 22q11.2DS attended mainstream education at the start of elementary school, there was a shift toward special education settings during high school.[76]

Psychosocial and Emotional Impact

Anxiety and depression were the most commonly reported psychosocial impacts among patients with rare kidney diseases and their caregivers.[25,26,30,31,34–36,42,44,48,51,53,54,59,62,70,72] Factors contributing to anxiety and depression included burden of caregiving responsibilities,[30,35,51] patients' loss of employment,[44,53,54] financial stress resulting from employment loss among caregivers of children,[51] and lack of future employment security for both patients[53,54] and caregivers.[41] Among 216 caregivers (91% female) of patients with sickle cell disease in Nigeria, 80% had self-reported episodes of depression.[51] A longitudinal (3-year) study of 72 caregivers of individuals with bladder exstrophy-epispadias complex in India found that 52% were concerned about their children's future fertility and marital prospects, leading to anxiety.[34] Caregivers of children who had initial surgery within 5 years of screening reported higher anxiety, which increased with subsequent surgeries ($P = 0.043$).[34] 82% of the participants reported that living with supportive families and interacting with cooperative school administrators or employers had protective effects against anxiety and stigma in the community. Over 36% of the participants identified a global surgical collaboration between US academic institutes and their treating hospital in India as a positive source of support.[34]

Emotional burden because of loss of work, as well as inability to engage in social activities with friends and family were reported in 2 studies.[30,59] A qualitative study which focused on the experiences of 72 female National Health Service (England) employees with SLE found that 29% had left their employment as a result of their disease, causing significant emotional and financial distress.[54] Among 139 caregivers of patients with ADPKD in Australia and countries in North America, Europe, Asia, and South America,[30] 74% reported negative impacts on their psychological and emotional wellbeing from the responsibilities of caregiving. Caregivers also expressed feelings of guilt and worry for having passed the disease to their children or the risk of passing it on to future children.[30] Feelings of guilt were commonly expressed by caregivers in 4 other articles examining socioeconomic burden of rare genetic kidney diseases.[26,27,70,75]

Out-of-Pocket Expenses and Affordability

Five articles reported out-of-pocket costs associated with rare kidney diseases.[26,28,43,73,74] Out-of-pocket costs generally accounted for a small proportion of direct healthcare costs and were mostly associated with copayments for therapies,[35,43,71,74] payments for ancillary devices such as hearing aids,[26] and transport costs related to medical appointments.[63,71] Intersectional disparity in the burden of out-of-pocket costs was reported in a qualitative study of 10 patients with SLE in the United States, where a lack of support for and high-costs linked to travel for medical appointments disproportionally impacted African-American women residing $>$ 80 miles from specialist facilities.[63]

Both direct and indirect expenditure were examined in a study of 45 patients and caregivers affected by nephrotic syndrome in the United States.[43] Out-of-pocket expenses were found to be much higher in patients with ESRD compared with patients without

ESRD. Median annual out-of-pocket costs in the cohort were $3464 ($844–$5865) per patient ($n = 28$ adult patients) and $1687 ($1035–$4763) per caregiver ($n = 17$ caregivers). Kidney transplants and special diets were 2 of the biggest drivers of out-of-pocket costs and out-of-pocket expenses varied by the type of insurance held. For non-ESRD adults, those with private insurance ($n = 15$) had greater expenses for medications, hospitalizations, and visits than those with at least some public insurance ($n = 3$). Similarly, caregivers of non-ESRD children with private insurance only faced higher medication expenses compared with those with public insurance. One participant who paid just $120 in out-of-pocket expenses annually attributed this low cost to supplementary coverage by a state-run program, which provided financial coverage for children with special health care needs and their families.

Financial constraints experienced as a result of rare kidney disease were reported by patients and caregivers in 12 articles.[25,26,30,32,35,43,51,54,57,63,70,74] Such constraints often led to delays in treatment[35,57,74] or choosing not to access treatment or diagnostic tests because of nonaffordability.[74] A study that explored the knowledge and burden of sickle cell disease among caregivers in Nigeria found that of the 216 study participants, over 25% had taken a loan to meet the expenditure because of their child's illness.[51] Caregivers of patients with ADPKD across 14 countries in North America, South America, Asia, Australia, and Europe reported draining personal savings to cover healthcare costs and expressed frustration at there being "no effective treatment or cure" and at their financing of healthcare, potentially resulting in no improvement in the patient's condition.[30]

DISCUSSION

This scoping review represents the first systematic assessment of the evidence of the socioeconomic burden of rare kidney disease on patients and caregivers. Although 53 studies were identified, these had a narrow geographic spread (75% of the studies were undertaken in countries of North America and Europe; 9% [5 of 53] were conducted in a low- or middle-income country). Only one-quarter (13 of 53) of all articles included rare disease cohorts with presentation limited to kidney involvement, 5 of which examined the socioeconomic impact of the most common rare kidney disease, ADPKD. Data on multisystem conditions, including SLE, SSc, and tuberous sclerosis complex, were more abundant, potentially reflective of the greater historical investment in their advocacy and awareness.[78,79]

Despite these limitations, the current body of evidence exposed a significant socioeconomic burden of rare kidney diseases characterized by substantial negative impact on human capital and lifetime societal costs. Such costs encompassed impaired employment and work productivity, educational advancement, psychosocial and emotional impact, care affordability, and out-of-pocket expenses. Our chosen scoping review methodology, and the largely descriptive nature of existing evidence, prevented the application of traditional monetary estimates of disease-related socioeconomic burden, including cost-of-illness methods. Previous research, characterizing the types of costs included in studies of socioeconomic burden has consistently noted that intangible costs borne by patients, their families, and caregivers, and the indirect costs associated with lost productivity, are less frequently assessed.[80–82] Although the use of patient and caregiver perspectives in burden of disease assessments may underestimate total societal costs,[83] their application is particularly relevant for rare diseases which require caregiver dedication, impose high nonmedical out-of-pocket costs, and for which certain therapies or services are not reimbursed by the public health care system or insurers.[84,85] It also suggests that conventional measures to promote universal health coverage, which focus on protection from the financial risk of direct medical costs, may be of limited impact in addressing the full socioeconomic burden of rare kidney diseases.

The interconnection of key contributors to the socioeconomic burden reported here provides a powerful illustration of the lifelong impact of rare kidney diseases. It reinforces a need for holistic models of patient and caregiver support, which extend across the course of life and include support in education, employment, and social services. Almost one-quarter of the included literature reported a substantial burden on education in children with rare kidney diseases, including school absenteeism,[26,31,35,43,51,58,70,73] interrupted or delayed education,[25,58,72,76] and impaired school performance.[25,36,48,73] Low education and poor physical and mental health have been shown to exacerbate the impact on employment.[86] This impact is underpinned by difficulties in retaining work for less educated individuals with poor physical health because of less job control or the presence of physically demanding work activities,[87,88] a need for tailored work arrangements,[87] and a requirement of substantial psychological resources to overcome the challenges of finding or retaining paid employment in the context of poor health.[89,90] Indeed, our findings clearly illustrate these subsequent employment-related impacts in those with rare kidney diseases, encompassing impaired work

productivity and work absenteeism,[24–29,40,44,49,52–58,60,61,64,67–70,72–74,77] reduced career advancement,[53,54,72] and early job discontinuation.[54,66,74] Evidence of such effects is also reported in the limited available literature exploring the impact of rare diseases on employment more broadly.[91,92] Owing to discrimination and marginalization faced by individuals with rare diseases in many work environments, it is crucial that policies to prevent or counter such behaviors are developed. Moreover, because of the multifaceted nature of health challenges faced by many with rare diseases, it is important that standardized methodologies for the assessment of work-related impact, which consider the common challenges linked to work disability, difficulties arising from rare diagnoses, distinctive medical symptoms, and the unique circumstances of individual patients are established.[93]

Our review identified 3 studies recommending the need for support from employers and colleagues at workplaces for individuals with rare kidney diseases and caregivers,[34,53,54] and 1 study recommended the importance of improved support and information for employers.[59] Similar findings have been reported in a systematic review that explored the determinants at the employer level that are associated with work and employment of workers with disabilities.[94] Moreover, we found limited evidence at the organizational level in relation to workplace policies or work accommodations, which is echoed in the existing literature.[94] Only 2 qualitative studies explored the employment experiences of individuals living with SLE, and reported that support from employers and colleagues at workplaces was a positive indicator to remain in work.[53,54]

Our findings highlight the substantial emotional, social, professional, and financial impact on caregivers of patients with rare kidney diseases and their families.[30,72] Caregiver distress was found to be significantly high in parents caring for children and adolescents with rare kidney diseases. Moreover, findings of parental guilt relating to genetically acquired rare kidney diseases[26,27,30,70,75] are echoed in the wider rare disease literature.[95] Interventional programs which follow a family-centered approach focusing on improving parental skills in coping with caregiving-related stress might help alleviate caregiver distress.[96] One such program is the CARE-FAM-NET program in Germany, which has been developed to close the existing gap in the psychosocial needs of families of children diagnosed with rare diseases.[97]

Although equity considerations remain poorly explored in studies to date, the available evidence suggests geographic and gender-based disparities in socioeconomic burden. Preprint data from the UK National Registry of Rare Kidney Diseases,[98] published following the completion of this review, show that children in the registry were more likely to reside in locations classified as more deprived (using the index of multiple deprivation score) than the general population, providing empirical evidence of the impact of a rare kidney disease diagnosis in a child on a family's financial position. In the single previous study examining travel burden (in an SLE patient cohort), women living further than 80 miles from their treating urban-based facility, were more likely to incur higher out-of-pocket costs to access ongoing specialist appointments.[63] Emerging evidence from both high-income (Germany)[71] and low-income (Nigeria)[51] settings indicates a disproportionate financial burden faced by female caregivers of children with rare kidney disease because of reductions in working hours to uphold caregiving responsibilities. Gender disparities (gender referring to socially constructed roles, behaviours, expressions and identities) have been highlighted in studies exploring the needs of caregivers of children with rare diseases more broadly, with mothers exhibiting higher levels of stress and emotional challenges associated with caregiving than male caregivers.[99,100] Earlier research examining the impact on education and employment remains largely biased by either convenience sampling or by a disproportionate number of female participants[53,54,58]; studies where sex- and gender-based analyses were possible, failed to do so.[76] Published estimates of direct and indirect financial costs of rare kidney disease[28,43,60] have, to date, not been sex-disaggregated. It is critical that future research in this area incorporates not only sex and (where possible) gender-disaggregated analyses but also examines other structural and social inequities, including race, ethnicity, domicile, education, and income to identify those population groups most vulnerable to the socioeconomic impact of rare kidney disease and inform tailored solutions.[101,102]

We found little evidence of coping strategies used by patients and caregivers affected by rare kidney disease. Where reported, these included the uptake of additional insurance policies to mitigate care-related out-of-pocket costs[43] and, for caregivers, drawing on emotional support from affected families and care providers.[34] Coping strategies have been previously explored in parents of children with chronic diseases,[103–106] including rare diseases[107]; and these strategies include seeking social support,[103,105,107] believing in the benefits of medical care,[104] communication with medical staff,[103,107] and prayer and religion.[103,105,107] Interestingly, information seeking has been reported as having both

positive[106] and negative[104] impacts on parental coping. Coping strategies in adults living with a rare disease remain underexplored and represent a notable evidence gap for the design of context-effective patients and caregiver support programs.

Limitations

A scoping review methodology was selected for this research to provide breadth rather than depth of information. Given that this was the first systematic assessment of the socioeconomic burden in rare kidney disease known to us, our objective was to provide a broad overview of the available evidence of this burden on patients and caregivers to highlight known areas of socioeconomic burden, identify evidence gaps requiring future research, and (where possible) suggest early intervention priorities. Nevertheless, the findings of this review must be considered with the inherent limitations of a scoping review, including the absence of methodological and risk of bias evaluations of the included studies and the inability to combine measurements of socioeconomic burden through meta-analyses. The previously mentioned narrow geographic coverage of available evidence, including the substantial absence of evidence from low- or middle-income settings, and the small number of studies focusing on conditions primarily involving the kidneys represent further limitations. Our restriction to English language studies may have omitted some evidence, particularly from low- or middle-income settings; this lack of evidence of disease burden reflect the limited data on rare disease prevalence and limited screening and diagnostic infrastructure in these settings.[108] Consequently, the findings reported here reflect the experience of only a limited number of populations, predominantly residing in settings with higher-resourced health systems and (somewhat) accessible diagnostic and treatment infrastructure. Further data collection and research are critical for understanding prevalence, incidence, and costs in low-resource settings, and geographic and socioeconomic variation within high-income settings. In addition, more targeted exploration of caregiver burden is warranted. Finally, because multisystem conditions predominated in the included studies, further targeted research is required to explore the socioeconomic burden in those impacted by rare diseases, in which the kidney is the primary affected organ.

CONCLUSION

The socioeconomic burden of rare kidney diseases extends beyond monetary aspects, profoundly impacting the lifelong well-being of patients and caregivers. The restricted body of existing literature illustrates the lifetime societal costs. However, significant gaps in our understanding of burden remain, particularly in lower-resource health systems, among traditionally marginalized populations, and for rare diseases in which kidney is the primary affected organ. To elucidate socioeconomic burden more comprehensively across global settings and within diverse populations, there is a pressing need for research involving patients with rare kidney diseases and their caregivers in low- and middle-income settings, and the disaggregation of data by age, sex and gender, education, socioeconomic status, and other key equity factors. In addition, recognizing that most rare kidney diseases have, until now, lacked appropriately approved and accessible therapies, further research and evaluation of social interventions and alternative care models to support nonhealthcare needs of patients and caregivers is critical. Finally, the lifelong impact of rare kidney diseases necessitates a paradigm shift in focus from patient numbers to societal burden to drive increased investment in patient- (and caregiver-) centric health care innovation.

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the decision to submit the manuscript for publication. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the participating organizations.

DATA AVAILABILITY STATEMENT

All the data resulting from this research are available in the main text or tables.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Search strategy for PubMed.

PRISMA Checklist.

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