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EDITORIAL COMMENTARY

What is the true burden of chronic kidney disease in children worldwide?

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Introduction

Chronic kidney disease (CKD) is recognized as a leading public health priority worldwide. The global prevalence of CKD is estimated at ~ 10% of the general population, affecting > 800 million adults worldwide among which about 4 million require kidney replacement therapy (KRT) [1]. The global increase in CKD is mainly driven by the increasing prevalence of diabetes, hypertension, obesity, and aging. Although mortality has declined in patients with kidney failure, the Global Burden of Disease (GBD) studies have shown that CKD is now a leading cause of worldwide morbidity and mortality [2]. In addition to being a major clinical problem, CKD causes economic and organizational concerns since KRT consumes a substantial proportion of health care resources. In this context, any medical intervention that may prevent the progression of CKD toward kidney failure is crucial. In adults, it has been shown that early detection of CKD and regular nephrology specialist care is associated with decreased morbidity and mortality.

In contrast to the adult population, in whom the prevalence of CKD has been systematically assessed worldwide, very little is known about the epidemiology of childhood CKD. Most of the epidemiological knowledge in children is derived from KRT registries like the ESPN/ERA Registry in Europe, the USRDS in the USA, or other registries [3–5]. Yet, it is important that childhood CKD is identified early, monitored, and treated properly, and that preventive measures addressing CKD progression are implemented. To this end, and to anticipate the pediatric nephrology workforce needs, we should improve our understanding and more precisely determine the true prevalence of CKD and its stages in the pediatric population.

Definition of CKD and its pitfalls in pediatric epidemiological studies

The diagnosis of CKD is established by estimating glomerular filtration rate (eGFR) from a filtration marker, such as serum creatinine or cystatin C, using various formulas, or by testing urine for the presence of protein or albumin (or a combination of these). Unfortunately, there is no optimal method that can accurately estimate GFR in children. Indeed, GFR varies according to age, sex, race, ethnicity, and size, which pose challenges in developing accurate eGFR equations in children, particularly in the early stages of kidney injury. Another limitation is the diversity of laboratory methods to determine serum creatinine or cystatin C. Nevertheless, the widespread standardization of creatinine and cystatin C measurement has led to the development of improved eGFR equations such as the revised Schwartz (CKiD) formulas, which are used globally in routine clinical practice and research [6, 7].

CKD was first defined by the 2002 KDOQI Guidelines and endorsed at the subsequent 2012 KDIGO Controversies Conference with some modifications [8, 9]. These classifications were applicable to children and have shown limitations but also benefits for the pediatric nephrology community. One may consider that the CKD grading system is based on arbitrary thresholds of eGFR, ignores age- and sex-related changes in GFR, only applies to children older than 2 years old, gives more weight to albuminuria while most children have non-glomerular diseases, and that stages 1–2 would be better defined by associated abnormalities rather than

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being classified as childhood CKD. However, the CKD classifications brought order to the chaos of nosology of CKD and were widely adopted, improved the understanding of the problem among pediatricians, increased the interest in systematic detection of kidney diseases, and stimulated clinical and epidemiological research on pediatric CKD [10, 11].

Pediatric studies assessing the prevalence of CKD have applied a variety of definitions of CKD, usually based on eGFR or serum creatinine thresholds (e.g., < 75 ml/min/1.73 m^2). In the past 10 years, however, several pediatric studies have followed the CKD guidelines and used eGFR alone to report the incidence and prevalence of CKD stages 3–5, whereas almost none has combined albuminuria and decreased eGFR to report CKD stages 1–5. Finally, to differentiate the true long-term condition of CKD from transient fluctuations in kidney function or from acute kidney injury, the definition of CKD includes a chronicity criterion (i.e., that low eGFR or elevated albuminuria should be observed for at least 3 months, thus requiring the presence of repeated measurements over time).

Current evidence on childhood CKD prevalence and study by Geylis et al.

Since CKD is most often asymptomatic initially, it is difficult to obtain reliable data on the early stages of pediatric CKD so that incidence and prevalence are very likely to be underestimated. Therefore, epidemiological data for CKD stages 2–5 are scarce in children and mainly based on KRT registries [3]. Although pediatric registries and cohorts using the K/DOQI or KDIGO classifications are emerging, only a small number of studies on the epidemiology of CKD stages 2–5 are available. Due to the lack of disease awareness, access to diagnosis, and data acquisition, the prevalence of kidney diseases in low-resource settings is even less well known [12]. For these countries, the data mainly come from reports of the main tertiary care centers and the true burden of pediatric CKD is widely underestimated or unrecognized.

Although inclusion criteria are variable, the available epidemiological studies [13–23], most of which are hospital-based and conducted in Europe in the past 25 years, estimate the prevalence of pediatric CKD stages 2–5 between 30 and 100 per million age-related population (pmarp) per year (Table 1). A low prevalence of CKD stages 3–5, of about 30 pmarp, was found in Japan but this was a survey sent to all institutions across the country with incomplete reporting of pediatric CKD cases aged < 15 years in 2010 [21]. Conversely, the prevalence was higher at about 90 pmarp in the UK but the study was conducted in a hospital setting with uncertainties about the geographical area covered [22]. In Kuwait, a higher prevalence of CKD of 330 pmarp was reported in children with GFR < 50 ml/min/1.73 m^2 between 1996 and 2003 [17], suggesting the role of genetic factors. A similar finding (prevalence of CKD stages 2–5 of 330 pmarp) was reported in Southern Israel in 2008 [23]. Although using different CKD definition and eGFR methods, these reports suggest that up to one in 10,000 children may have CKD. However, all hospital-based studies suffer from underestimation of the prevalence since only patients with overt CKD, followed in a pediatric nephrology center, are captured in the study and included in the numerator.

There are only a limited number of population-based studies in the general pediatric population, but they support a very different picture than suggested by the current hospital-based studies. Indeed, a much higher prevalence of undiagnosed CKD stages 2–5 in children (usually defined as eGFR < 75 ml/min/1.73 m^2), of around 1%, has been reported in cross-sectional studies in Turkey, Iran, and China [24–26], suggesting a possibly 100-times greater prevalence of CKD than that estimated in hospital-based studies. In the Turkish and Chinese studies, the prevalence of low eGFR < 60 ml/min/1.73 m^2, potentially consistent with the presence of CKD stage 3, was 0.25%. Among US adolescents aged 12 to 18 years who participated in the National Health and Nutrition Examination Surveys, the prevalence of low eGFR < 60 ml/min/1.73 m^2 was 0.3% in 1988–1994 and 0.9% in 2009–2014, and between 3 and 4% of the screened adolescent population had albuminuria [27]. In none of these studies, however, was a confirmation of abnormal eGFR indicating CKD stage 3 performed with two eGFR measurements at least 3 months apart. All these cross-sectional surveys with single time-point determination of kidney function may therefore lead to an overestimation of the true prevalence of CKD. However, the latter rates of low eGFR in children are consistent with the global prevalence estimates of CKD (1.8–2.6%) reported in young adults aged 20–29 years [28]. Besides national health surveys, another approach to estimate the prevalence of overt chronic conditions is to identify cases from administrative data sources such as health insurance records. Based on data from a single US health insurance company including almost 2 million individuals from the pediatric age group (< 21 years), the prevalence of children and adolescents with a CKD diagnosis code (ICD-9 and ICD-10) was 27 per 10,000 (0.27%) in 2016 [29], a figure seemingly close to other population-based studies. In this report, the prevalence of CKD was actually comparable to that of pediatric diabetes mellitus (31 per 10,000).

In a recent issue of *Pediatric Nephrology*, Geylis et al. estimated the population-based prevalence of pediatric CKD in Southern Israel using administrative and hospital laboratory data [30]. The strength of this study was to

Table 1 Selected studies reporting the prevalence of CKD in children

Study (reference)	Country, period	Study design	CKD definition	Population covered (age)	Prevalence
Deleau (13)	France, 1975–1990	Hospital-based annual surveys	SCr > 133 µmol/L in children < 2 years and SCr > 175 µmol in children ≥ 2 years	Regional (0–15 years)	Increased from 15 to 37 pmarp
Esbjörner (14)	Sweden, 1986–1994	Hospital-based surveys	eGFR < 30 mL/min/1.73 m^2	National (0.5–16 years)	Increased from 47 to 59 pmarp
Lagomarsimo (15)	Chile, 1996	Hospital-based cross-sectional survey	SCr 2 times the upper limit of normal or eGFR < 30 mL/min/1.73 m^2	National (0–17 years)	43 pmarp
Ardissino (16)	Italy, 1990–2000	Hospital-based multicenter annual surveys	eGFR < 75 mL/min/1.73 m^2	National (0–19 years)	75 pmarp
Al-Eisa (17)	Kuwait, 1996–2003	Hospital-based single center study	eGFR < 50 mL/min/1.73 m^2	National (0–15 years)	329 pmarp
Areses Trapote (18)	Spain, 2008	Hospital-based multicenter registry	CKD stages 2–5	National (0–17 years)	71 pmarp
Mong Hiep (19)	Belgium, 2001–2005	Hospital-based multicenter registry	CKD stages 3–5	National (0–19 years)	56 pmarp
Peco-Antic (20)	Serbia, 2000–2009	Hospital-based multicenter annual reports	CKD stages 2–5	National (0–18 years)	96 pmarp
Ishikura (21)	Japan, 2010	Hospital-based multicenter cross-sectional survey	CKD stages 3–5	National (0–15 years)	30 pmarp
Kim (22)	UK, 2005–2009	Hospital-based single center study	CKD stages 3–5	Regional (0–15 years)	Increased from 15 to 37 pmarp (mean 90)
Landau (23)	Israel, 1994–2008	Hospital-based single center study	CKD stages 1–5	Regional (0–19 years)	795 pmarp
Soylemezoglu (24)	Turkey, 2007–2008	Population-based cross-sectional study	CKD stages 3–5 and eGFR < 75 mL/min/1.73 m^2	Nationally representative sample, $n = 3622$ (5–18 years)	0.26% (CKD 3–5) or 0.94% (eGFR < 75)
Song (26)	China, 2009	Population-based cross-sectional study	CKD stages 3–5 and eGFR < 75 mL/min/1.73 m^2	Nationally representative sample, $n = 793$ (7–18 years)	0.25% (CKD 3–5) or 1.01% (eGFR < 75)
Saydah (27)	USA, 1988–2014	Population-based repeated cross-sectional studies	eGFR < 60 mL/min/1.73 m^2 and albuminuria	Nationally representative sample, $n = 9225$ (12–18 years)	Increased from 0.32% in 1988–1994 to 0.91% in 2009–2014
USRDS (29)	USA, 2016	Population-based administrative database study	ICD-9 and ICD-10 CKD codes	National single commercial health insurance data, $n = 1{,}970{,}375$ (0–21 years)	0.27%
Geylis (30)	Israel, 2001–2015	Population-based single center study	≥ 2 eGFR values < 60 ml/min/1.73 m^2	Regional administrative health records, $n = 79{,}374$ (0–17 years)	882 pmarp

CKD, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *SCr*, serum creatinine; *pmarp*, per million age-related population

reuse all serum creatinine measurements available after 2 years of age in the electronic health records to define CKD as ≥ 2 eGFR values under 60 ml/min/1.73 m^2 at least 3 months apart, therefore including the criterion of chronicity, which was ignored by the other population-based studies. The estimated prevalence of children who fulfilled the "ever CKD" criteria in 2019 was 1033 pmarp (0.1%). The prevalence of children still classified as having CKD at last follow-up was slightly lower (882 pmarp) and may be overestimated since the denominator only included children with at least one serum creatinine measurement available (more than half of the population). Another interesting finding of this study is that a GFR slope of − 1 ml/min/1.73 m^2 per year could be derived suggesting that it may take decades before these children with mild to moderate CKD (on average 12 years old and eGFR of 50 ml/min/1.73 m^2) reach advanced CKD or kidney failure [30].

Importance of awareness and advocacy in pediatric CKD

On the basis of hospital-based studies examining the prevalence of pediatric CKD (ranging from 0.3 to 1 per 10,000 children) and the results of the few population-based studies suggesting a much higher prevalence (from 1 to 10 per 1000 children), the current total number of children and adolescents affected by CKD stages 2–5 worldwide could be extrapolated to exceed 2 million CKD cases in a global population of 2 billion children. This is a worrisome figure that is in the same range as the estimated number of childhood cancers, the estimated number of children with type 1 diabetes, and 10 times higher than the number of children affected by cystic fibrosis. CKD is therefore one of the most common pediatric noncommunicable diseases. However, contrary to the aforementioned diseases, the public awareness, level of policy attention, and investment required for pediatric CKD are still very poor. This is partly due to the complexity of pediatric CKD which comprises many etiologies (often rare diseases) and covers a wide spectrum of presentations from a usually silent disease in its early stages to the devastating impact of kidney failure on quality of life and life expectancy. As a result, the uptake of the concept of pediatric CKD by the public, physicians, and health authorities is far too low. The lack of public and policymakers' awareness of pediatric kidney diseases and the consequences of delays in diagnosis and adequate treatment are major contributors to alarming situations. For example, the rate of late presentation of pediatric CKD, defined as first presentation to pediatric nephrology care with kidney failure, is unacceptably high (> 40%), especially in low- and middle-income countries, reflecting the lack of timely diagnosis and referral to pediatric kidney care [31]. Another situation of long-term concern is the association of a history of clinically evident CKD, albeit mild, in childhood with a higher risk of kidney failure at a young age in adulthood, which further highlights the demand for better prevention and treatment by pediatric nephrologists [32]. Finally, it is well demonstrated that public investment in specialized pediatric kidney care and multidisciplinary expertise is worth the cost to optimize outcomes such as access to best treatment and survival [33, 34].

We need to do more to raise awareness of and advocate about pediatric CKD to improve health outcomes. This calls for collecting more data from population-based CKD registries and cohorts not only including KRT but also earlier stages of CKD in which kidney failure may be delayed or prevented, and evaluating the impact of population screening interventions in children with risk factors of CKD. Such strategies will allow providing simple and reliable statistics for communication on the true burden of pediatric kidney diseases, and effective lobbying of professional organizations like IPNA to advance kidney health in children everywhere.

Declarations

Competing interests The authors declare no competing interests.

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