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Social Deprivation and Incidence of Pediatric Kidney Failure in France

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Introduction: Approximately 8 per million children and young adults aged < 20 years initiate kidney replacement therapy (KRT) per year in France. We hypothesize that social deprivation could be a determinant of childhood-onset kidney failure. The objective of this study was to estimate the incidence of pediatric KRT in France according to the level of social deprivation.

Methods: All patients < 20 years who initiated KRT from 2010 to 2015 in metropolitan France were included. Data were collected from the comprehensive French registry of KRT French Renal Epidemiology and Information network (REIN). We used a validated ecological index to assess social deprivation, the 2011 French version of the European Deprivation Index (EDI). We estimated the age standardized incidence rates according to the quintiles of EDI using direct standardization and incidence rate ratio using Poisson regression.

Results: We included 672 children with kidney failure (58.6% males, 30.7% with glomerular or vascular disease, 43.3% starting KRT between 11 and 17 years). 38.8% were from the most deprived areas (quintile 5 of EDI). The age standardized incidence rate increased with quintile of EDI, from 5.45 (95% confidence interval [CI] = 4.25–6.64) per million children per year in the least deprived quintile to 8.46 (95% CI = 7.41–9.51) in the most deprived quintile of EDI (incidence rates ratio Q5 vs. Q1 1.53-fold; 95% CI = 1.18–2.01).

Conclusion: This study showed that even in a country with a universal health care system, there is a strong association between the incidence of pediatric KRT and social deprivation showing that social health inequalities appear from KRT initiation. This study highlights the need to look further into social inequalities in the earliest stage of chronic kidney disease (CKD).

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CKD is a rare but devastating condition in children. In 2018, the age standardized incidence of KRT for kidney failure in the pediatric population varied from < 1 to 14 per million children in patients aged < 20 years, across different countries worldwide,[1] with an incidence at 8 per million in France.[2] In particular, it has been shown that the considerable variations in age standardized incidence rate between different European countries were associated with national income defined as country's gross domestic product and with public health expenditure.[1]

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The burden of CKD falls disproportionately upon adults with lower socioeconomic status, who have a higher prevalence of advanced CKD and kidney failure, lower access to KRT, and poorer outcomes.[3,4] Lower socioeconomic status in high-income countries such as United Kingdom,[5] and social determinants of health such as health insurance coverage and education level have been associated with an increased prevalence of CKD.[6] Social deprivation was also associated with higher incidence of acute kidney injury in adulthood.[7] In the pediatric population, given the age specific distribution of causes of CKD (mainly structural abnormalities and hereditary nephropathies), we could assume that the environment has a limited effect whereas genetic determinants have a stronger impact on the incidence of kidney failure. However, in a recent review, Krissberg *et al*.[8] suggested that socioeconomic differences generate risk factors associated with the development and progression of pediatric CKD. Furthermore, Boynton *et al*.[9] found a crude association between neighborhood poverty and progression to kidney failure in US children and an association with hospitalizations and emergency department use after adjustment. This is consistent with our 2 recent previous studies in which 40% of the children initiating KRT in metropolitan France belonged to the most deprived quintile of a validated ecological EDI,[10] which was associated with KRT modality,[11] urgent-start of KRT,[11] and graft survival.[12] We hypothesize that social deprivation is also associated with CKD progression at earlier stages and thus ultimately with the incidence of kidney failure at pediatric age. However, to our knowledge, no study ascertained whether the incidence of KRT varies with social deprivation in the pediatric population, in particular in countries where access to care is intended to be equal. Our objective was thus to estimate and compare the incidence of pediatric KRT according to the level of social deprivation in metropolitan France where universal health insurance system covers 100% of the costs of CKD and is one of the organization for economic cooperation and development countries with the lowest out-of-pocket payment for chronic diseases.

METHODS

Population Outcome and Data Source

We included all patients who initiated KRT before the age of 20 years, from 2010 to 2015, in metropolitan France (European territory of France). KRT was defined as initiating chronic dialysis or receiving a kidney transplant whichever occurred first between January 1, 2010 and December 31, 2015. Data for KRT were collected from the REIN registry which includes details on all KRT performed in France since 2002.[13] All French centers gave their approval to participate in the study. The REIN registry has the approval of the French data protection authority (Commission Nationale de l'Informatique et des Libertés) and a waiver of ethics approval. To estimate age standardized incidence we used census data from 2010 to 2015, by age group (0–2, 3–5, 6–10, 11–17, and 18–19 years), from the French National Institute of Statistics and Economic Studies database.

Social Deprivation Assessment

We used the 2011 French version of the EDI.[10,14] The EDI was assessed at the residential address of the child at the registration on the transplant waiting list because almost all children with CKD in France are registered on the waiting list. The listing process is based on a national protocol that applies in all centers, virtually all pediatric patients are listed, and there is no major kidney shortage.

EDI was built from the 2011 French population census data and from a 2011 European survey (European Union Statistics on Income and Living Condition) about social deprivation.[15] The EDI is a continuous score considering individuals' cultural and social environments. It is equal to the weighted sum of 10 binary variables based on the percentage, in the neighborhood, of (i) overcrowded housing, (ii) housing with no access to a bath or a shower, (iii) household without access to a car, (iv) no executive nor intermediate occupation, (v) single-parent household, (vi) household with 6 or more persons, (vii) unemployed people, (viii) household nonowners, (ix) persons without the French citizenship, and (x) persons with less than the first stage of tertiary education level.[10] Geographical delimitation of the neighborhood was defined by a small geographical unit called îlots regroupés pour l'information statistique ([IRIS], French small geographical unit) which has been developed by the French National Institute of Statistics and Economic Studies to divide the country into units of equal size of about 2000 residents, in order to prepare population census. The quintiles of the EDI correspond to the French 2011 IRIS, quintile 5 representing the most deprived areas. In addition to the EDI corresponding to the residential address of the children, we also constructed a binary variable reflecting the urban/rural environment of the children. According to the French National Institute of Statistics and Economic Studies, an urban environment was defined as a municipality or group of municipalities with a continuously built up area of at least 2000 inhabitants.

Estimation and Comparison of KRT Incidence According to EDI Quintiles

Crude incidence rates for each quintile of EDI (determined from the French 2011 IRIS) were estimated by dividing the total number of cases observed between 2010 and 2015 in each quintile by the sum of person-years in each quintile. These rates and their 95% CI were then standardized on age using a direct standardization method (Supplementary Methods S1). The age groups chosen were those available in census data over the entire study period, i.e., 0 to 2 years, 3 to 5 years, 6 to 10 years, 11 to 17 years, and 18 to 19 years. We also used Quasi-Poisson regression, a generalization of the Poisson regression accounting for over-dispersion, to estimate the incidence rate ratios by quintiles of EDI (also determined from the French 2011 IRIS), adjusted for age. We used the same age categories as above for the standardization, and the number of person-years as an offset term. A likelihood ratio test was also used to test the overall association between incidence rates and the quintiles of EDI, adjusted for age.

Due to incorrect or missing addresses in some patients, we were unable to assign quintiles of EDI to 8.8% of the study population. We thus imputed the missing quintiles using multiple imputations (R package MICE; Supplementary Methods S2) and we estimated the incidence rates and calculated their standard errors based on Rubin's rules.[16] We performed a sensitivity analysis on complete cases.

The analyses were carried out with R-3.6.1 and Excel softwares.

Geographic Distribution of KRT Incidence and of Deprivation

We described the geographical distribution of deprivation using the quintile of EDI assigned to each IRIS. We represented on another map of metropolitan France both the deprivation and the age standardized incidence of KRT, but at a larger geographical area than IRIS because pediatric kidney failure is a rare condition which cannot be accurately represented at the IRIS level. We chose the French department level, which is one of the official administrative divisions of France (96 departments in metropolitan France).[17,18] To represent the level of deprivation in each department, we first derived the proportion of individuals aged less than 20 years living in the quintile 5 of EDI, and then categorized the proportion into 5 categories using Jenks' natural thresholds (or natural breaks) method.[19] The bounds of the classes were thus defined by minimizing the intra class variances and maximizing the inter class variances of the indicator. We estimated the correlation between the proportion of patients in quintile 5 and the age standardized incidence rate with Kendall tau coefficient. The mapping was carried out using QGIS 2.18.28 software.

RESULTS

Cohort Description

Among the 672 included patients who initiated KRT before the age of 20 years between 2010 and 2015 in metropolitan France, 58.6% were male, 43.3% were between 11 and 17 years old at start of KRT, the majority lived in urban areas (79.6%) (Table 1). The most common causes of kidney failure were glomerular or vascular diseases (30.7%) followed by congenital anomalies of kidney and urinary tract (29.2%). Patients started KRT with hemodialysis in 53.9% of cases and 21.9% received a preemptive kidney transplant. The children from the most deprived quintile (quintile 5) represented 38.8% of the sample, whereas between 12 and 20% of patients were distributed in each other quintile (quintiles 1 to 4). The patients living in the most deprived areas (quintile 5) had more frequently glomerular/vascular disease (35.7% vs. 24.7%), less congenital anomalies of kidney and urinary tract (26.0% vs. 36.4%), started more often KRT with hemodialysis (59.1% vs. 41.6%) and lived less in rural areas (2.8% vs. 31.1%) than the least deprived children (Table 1).

Socioeconomic Deprivation and the Incidence of KRT

The overall crude incidence rate of KRT per million children years was 7.20 (95% CI: 6.66–7.75) (Table 2). When comparing quintiles of deprivation, a clear incidence gradient appeared for all indicators. The crude incidence rate (per million children-years) increased from 5.49 (95% CI: 4.31–6.66) in the least deprived quintile (quintile 1) to 8.54 (95% CI: 7.49–9.58) in the most deprived quintile (quintile 5). This increase remained after the direct age standardization of the incidence rate: 5.45 (95% CI: 4.25–6.64) in quintile 1 versus 8.46 (95% CI: 7.41–9.51) in quintile 5 (Table 2). After adjustment for age, the quintiles of EDI were also statistically significantly associated with the incidence rates ratio of KRT (P value = 0.005). The incidence rates of KRT was 1.40-fold (95% CI: 1.04–1.89) and 1.53-fold (95% CI: 1.18–2.01) higher in most deprived quintiles (quintiles 4 and 5) compared to the least deprived quintile (quintile 1), respectively (Table 2). We found similar results on complete cases, i.e. without imputation of missing quintiles (Supplementary Table S1).

Geographic Distribution of Deprivation and KRT

Most deprived IRIS were mainly concentrated in Paris and its suburbs, as well as in the North and Southeast

Table 1. Characteristics of incident pediatric patients with KRT between 2010 and 2015 in metropolitan France according to EDI quintiles (REIN registry 2010–2015)

		EDI $n = 613$				
	All children $n = 672$	Quintile 1 (least deprived) $n = 77$ (12.6%)	Quintile 2 $n = 88$ (14.4%)	Quintile 3 $n = 91$ (14.8%)	Quintile 4 $n = 122$ (19.9%)	Quintile 5 (most deprived) $n = 235$ (38.3%)
Characteristics	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Male	394 (58.6)	43 (55.8)	54 (61.4)	54 (59.3)	67 (54.9)	141 (60.0)
Age at KRT initiation (yr)						
0–2	94 (14.0)	14 (18.2)	14 (15.9)	15 (16.5)	9 (7.4)	31 (13.2)
3–5	56 (8.3)	7 (9.1)	11 (12.5)	4 (4.4)	11 (9.0)	19 (8.1)
6–10	83 (12.4)	10 (13.0)	9 (10.2)	15 (16.5)	20 (16.4)	23 (9.8)
11–17	291 (43.3)	36 (46.8)	36 (40.9)	36 (39.6)	57 (46.7)	110 (46.8)
18–20	148 (22)	10 (13.0)	18 (20.5)	21 (23.1)	25 (20.5)	52 (22.1)
Context of rural environment (missing = 55)	126 (20.4)	23 (31.1)	31 (36.0)	32 (36.4)	33 (30.0)	6 (2.8)
Primary disease						
CAKUT	196 (29.2)	28 (36.4)	26 (29.5)	30 (33.0)	40 (32.8)	61 (26.0)
Hereditary nephropathy	130 (19.3)	13 (16.9)	15 (17.0)	21 (23.1)	26 (21.3)	50 (21.3)
Glomerular/vascular disease	206 (30.7)	19 (24.7)	27 (30.7)	23 (25.3)	30 (24.6)	84 (35.7)
Other/Unknown	140 (20.8)	17 (22.1)	20 (22.7)	17 (18.7)	26 (21.3)	40 (17.0)
Modality of first KRT						
Hemodialysis	362 (53.9)	32 (41.6)	42 (47.7)	42 (46.2)	71 (58.2)	139 (59.1)
Peritoneal dialysis	163 (24.3)	26 (33.8)	21 (23.9)	20 (22.0)	26 (21.3)	54 (23.0)
Preemptive transplantation	147 (21.9)	19 (24.7)	25 (28.4)	29 (31.9)	25 (20.5)	42 (17.9)
Calendar yr of KRT initiation						
2010	111 (16.5)	10 (13.0)	17 (19.3)	13 (14.3)	19 (15.6)	42 (17.9)
2011	107 (15.9)	10 (13.0)	11 (12.5)	22 (24.2)	14 (11.5)	36 (15.3)
2012	97 (14.4)	12 (15.6)	15 (17.0)	13 (14.3)	17 (13.9)	33 (14.0)
2013	114 (17.0)	17 (22.1)	13 (14.8)	10 (11.0)	22 (18.0)	41 (17.4)
2014	103 (15.3)	9 (11.7)	15 (17.0)	18 (19.8)	20 (16.4)	36 (15.3)
2015	140 (20.8)	19 (24.7)	17 (19.3)	15 (16.5)	30 (24.6)	47 (20.0)

CAKUT, congenital anomalies of the kidney and urinary tract; EDI, European Deprivation Index; KRT, Kidney Replacement Therapy; REIN, French kidney replacement therapy registry.

of metropolitan France (Figure 1). Figure 2 shows a similar distribution of deprivation at the department level, with a proportion of children living in quintile 5 ranging from 2% to 88% depending on the department. The age standardized incidence rates were also heterogeneous across the departments (Figure 2), ranging from 0 to 15.27 children initiating KRT per million person years. However, no correlation emerged from the visual inspection of Figure 2 or from Kendall's correlation coefficient (tau = 0.06, $P = 0.43$) between the level of deprivation of a department and its age standardized KRT incidence.

DISCUSSION

This study found a social gradient in the incidence of pediatric kidney failure in metropolitan France, with a significantly higher age standardized incidence rate of KRT in the most deprived geographic areas according to the EDI.

Table 2. Crude incidence (per 1 million children per year), direct age standardized incidence rates (per 1 million children per yr), incidence rate ratios and of pediatric kidney replacement therapy according to social deprivation assessed by EDI quintiles (REIN registry 2010–2015)

	Cases (%)	Population[a] (%)	Crude rate[b] (95% CI)	Age standardized rate[b] (95% CI)	Incidence rate ratio[c] (95% CI)
Overall	672	93291184	7.20 (6.66; 7.75)	7.26 (6.71; 7.81)	
EDI Quintiles (imputed, $n = 672$)					
1 (least deprived)			5.49 (4.31; 6.66)	5.45 (4.25; 6.64)	Ref
2			6.35 (5.08; 7.61)	6.43 (5.12; 7.74)	1.17 (0.86; 1.62)
3			6.67 (5.36; 7.97)	6.54 (5.21; 7.88)	1.23 (0.90; 1.69)
4			7.86 (6.53; 9.18)	7.58 (6.27; 8.89)	1.40 (1.04; 1.89)
5 (most deprived)			8.54 (7.49; 9.58)	8.46 (7.41; 9.51)	1.53 (1.18; 2.01)

CI, confidence interval; EDI, European Deprivation Index; IRR, incidence rate ratio; KRT, Kidney Replacement Therapy; REIN ,French kidney replacement therapy registry.
[a]children-year
[b]per million children per year
[c]estimated by a Quasi-Poisson regression adjusted for age (five categories) using multiple imputation for missing EDI; *P* value = 0.005 (likelihood ratio test for the association between deprivation and incidence)

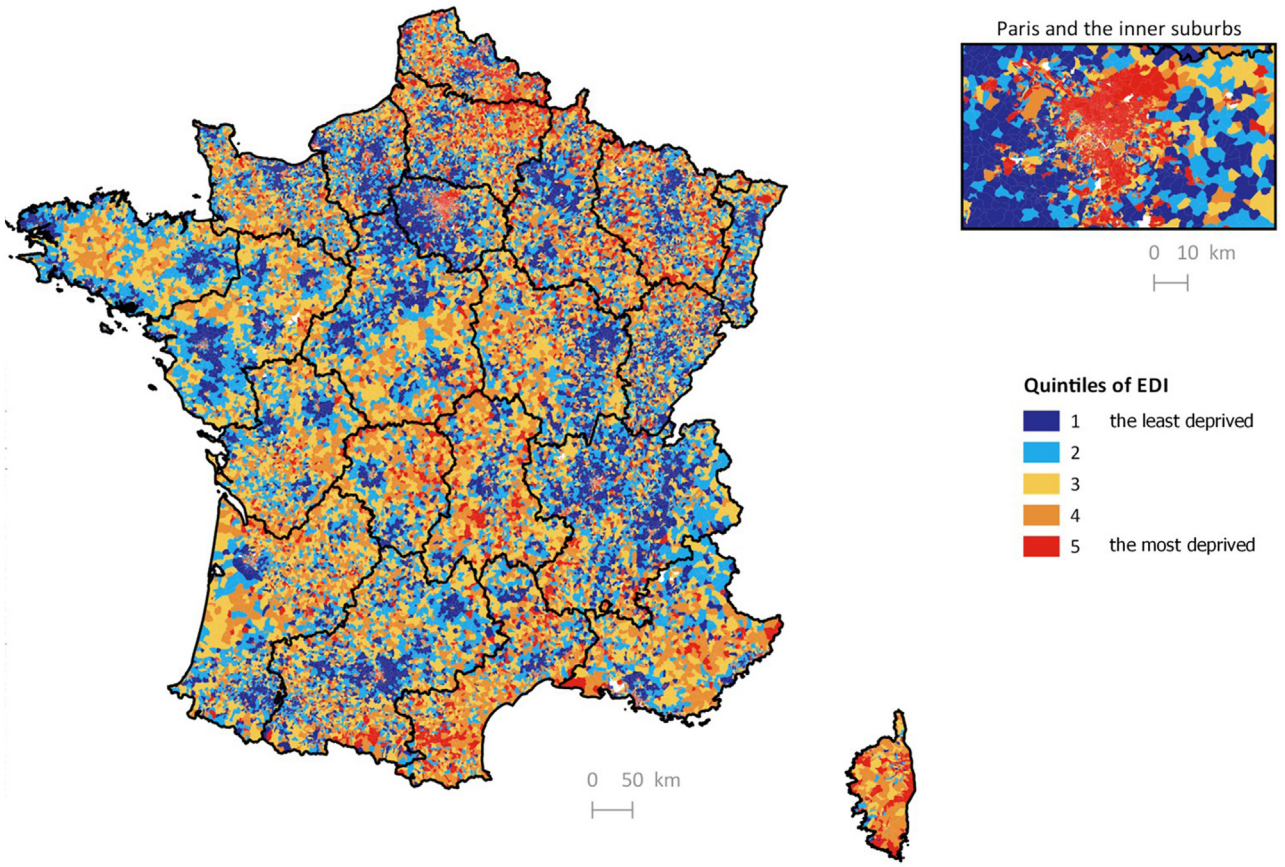

Figure 1. Spatial distribution of 2011 French version of European Deprivation Index by IRIS (Sources: INSEE data, REIN 2010-2015, U1086 INSERM UCN "Anticipe", Caen, France). [a]per million children per year

The CKD study in the United States has suggested that the progression of CKD to kidney failure could be faster in the most socially disadvantaged children.[20,21] In North America and Australia, children with CKD stages 1 to 5 were ∼3 times more likely to be in poorer or worse health when parents were of poor socioeconomic status.[22,23] In adult patients, deprivation has also been associated with severity of CKD in the US and the UK,[3,24,25] with the most deprived patients having a higher risk of reaching CKD stages 4 and 5.[4] In the US in particular, variations in incidence or prevalence of kidney failure have been partly explained by socioeconomic status.[26] Studies in adults have also shown that deprivation in the neighborhood was associated with the risk of kidney failure independently of individual deprivation variables in Sweden,[27] with the degree of proteinuria in the UK,[28] and with mortality in the US.[29] In Denmark, Hommel *et al.*[30] found that age- and sex-standardized incidence rates of KRT were significantly higher among the most deprived adults (lower education and income) compared with the least deprived individuals. In France, geographical differences in adult kidney failure have also been partly explained by deprivation and characteristics of the patients' geographical area.[31,32]

The social gradient found in our study strengthens the evidence that social inequalities might even exist in earlier stages of pediatric CKD, which could be partly explained by disparities in access to care. Our study conducted at the initiation of KRT corresponds to the first contact with the healthcare system for many children. Late referral to a nephrologist is one of the main reasons given for rapid progression to kidney failure and subsequently delayed access to waitlisting and preemptive transplantation[33–35] but the association between late referral and social deprivation is yet not clear. In the United Kingdom, social deprivation and geographic location were not associated with late referral, but deprivation was strongly associated with access to preemptive kidney transplantation in children.[36] We also previously shown that social deprivation is not only associated with the incidence of kidney failure but also with the modality of KRT (i.e., lower use of peritoneal dialysis and lower access to preemptive transplantation in the most deprived areas).[11]

One potential explanation of the observed association between deprivation and KRT incidence could be a lower access to care in most deprived population because of a higher distance between the children's home and the hospital or place of care. Indeed, distance

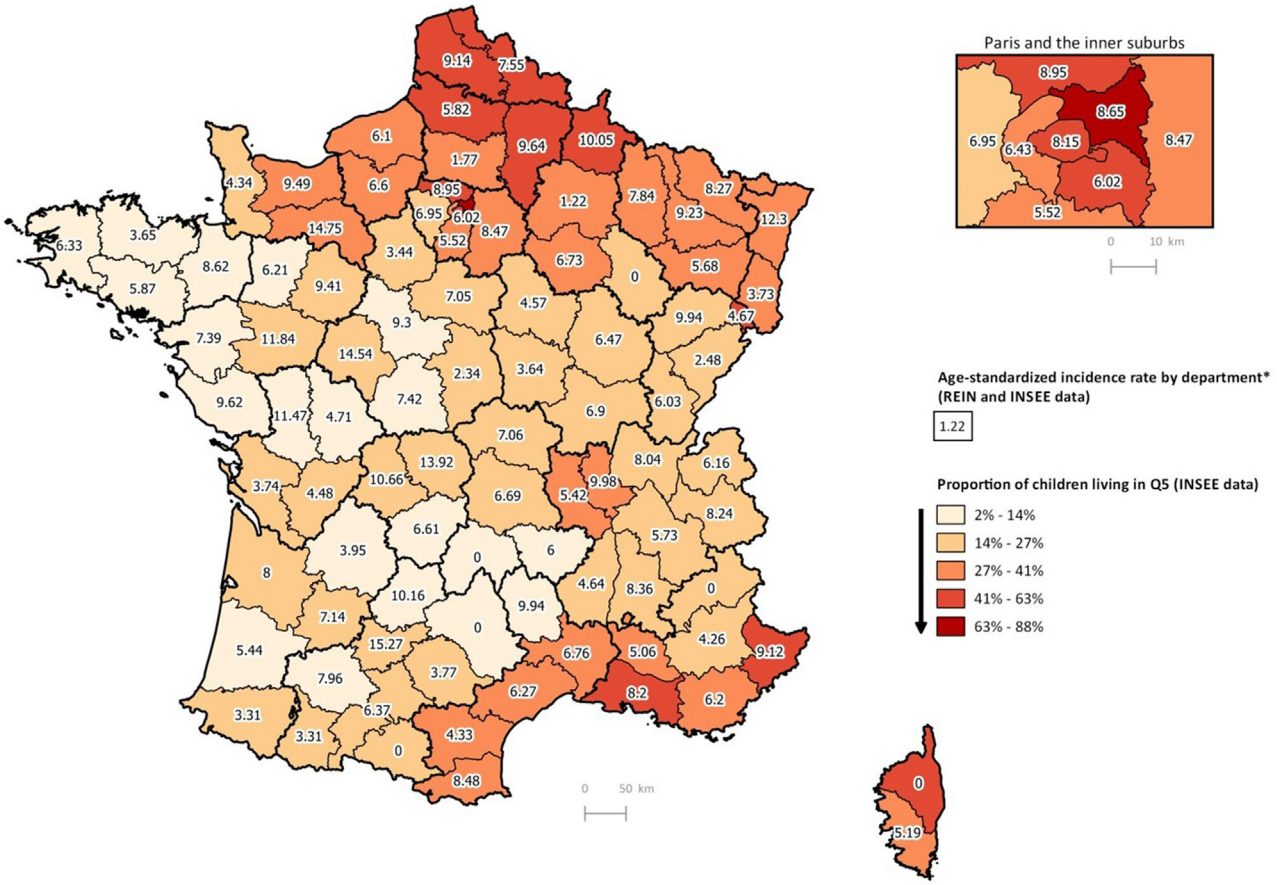

Figure 2. Indicator of social deprivation by administrative department, and distribution of age-standardized incidence rates of pediatric kidney replacement therapy by administrative departments, 2010-2015 (sources: REIN registry and INSEE data).

is a factor favoring inequalities in access to care and is often correlated with low socioeconomic levels due to the additional costs incurred by travel, explaining their delayed treatment.[37] However, in France, health insurance covers 100% of travel costs for CKD patients and < 3% of the most deprived children lived in the rural environment potentially far from large tertiary centers. Thus, distance from a tertiary care center does not seem to explain our results.

Another potential explanation could be that deprivation may have an impact on health care earlier in the CKD course, with poorer management of CKD when diagnosed, including lower health literacy, treatment adherence issues, etc., resulting in faster progression to kidney failure and lower preparation for planned KRT.[38–42] Poorer health literacy, lower adherence to treatment, and potential delayed diagnosis could explain the higher incidence of glomerular disease we observed in higher deprivation areas. Indeed, when treated in time, glomerular diseases can be treated or at least mitigated. It is also possible that lifestyle behavior, dietary patterns, and environmental factors, such as air pollution or endocrine disruptors, have a greater role in CKD progression among the most disadvantaged patients and families, as suggested in the adult population.[43,44] In the pediatric population, the socio-educational and family context is of critical importance. Learning to live with a chronic disease is an upheaval for the child but also for the family who must reorganize her life, cope with, and support the sick child. Although social autonomy (which defines the individual's ability to impact their care) characterizes adulthood, in childhood, especially at a very young age, the family is essential in managing the disease. However, not all family contexts can contribute to optimal management that would slow the progression of CKD and thus delay the need of KRT. Financial issues leading to disparities in healthy food , lack of time, or limited health literacy,[45] alone or simultaneously, are factors that can contribute to complicated child development and can generate socially compartmentalized developmental trajectories, irrespective of the context of chronic illness.[46] In some studies, the authors refer to this as childhood adversity, which appears to impact, for example, the mental health of the children concerned.[47,48] This rather ecosystem approach echoes Dahlgren and Whitehead's model of the determinants of health.[49] Thus, to reduce

inequalities of health, particularly in the occurrence of pediatric kidney failure, all these determinants should be taken into account as early as possible.

Our study has strengths and limitations. We used an exhaustive population of incident cases between 2010 and 2015 recorded in the REIN registry, a comprehensive nationwide registry of all adult and pediatric patients receiving KRT. However, we had some missing data on EDI because of incorrect or missing addresses in some patients, potentially because they were not yet on the waiting list. However, the process of registration on the list of centers is not a priori a major cause of disparities in access to pediatric transplants in France. Besides, as in our previous study on the association between deprivation and the different indicators at KRT initiation such as KRT modality, dialysis modality, urgent start of dialysis and late referral to a nephrologist, imputation of quintiles of EDI on the same population yielded similar results.[11] Moreover, the EDI was measured at the registration on the transplant waiting list but not at the KRT initiation. However, we assumed that this did not have a significant impact on our results because there were likely few address changes within this short time period (about 7 months in France) and people tend to move within the same deprivation quintile.

EDI is an ecological index that has several limitations (potential ecological bias, measured at only at the registration on the waiting list) but its derivation at the smallest French administrative geographical level allowed us to account for several variables to assess deprivation in the close neighborhood of children. However, that small geographical area used for the derivation of EDI did not allow us to investigate its spatial association with the incidence of a rare condition such as pediatric KRT.

To investigate the spatial association, we therefore used a larger geographical area (the French department) and thus derived the percentage of pediatric general population living in the quintile 5 of EDI (the most deprived areas) in the department. Yet, no clear spatial relationship appeared, but our indicator on the French administrative department level may not be adequate to study the spatial association between deprivation and incidence of pediatric KRT because of the scarcity of the event. Further spatial analysis using more appropriate indicator or geographical unit may be required. Another limitation is that we could not standardize on sex, because census data for pediatric population were not available. Only age standardization could be performed. Lastly, we acknowledge that the lack of data on ethnicity is an important limitation due to the known interaction between social deprivation and ethnic background. However, the proportion of people without French citizenship in the neighborhood contributes to the construction of the EDI, and data from the French National Institute of Statistics and Economic Studies showed that this proportion was higher in the most deprived quintile of EDI (unpublished data).

CONCLUSION

To conclude, our results suggest an association between social deprivation and pediatric KRT incidence in France, despite universal coverage by national health insurance. A social gradient appeared when estimating different incidence measures according to deprivation quintiles. Although further studies are needed in earlier stages of CKD to investigate whether these findings at KRT initiation reflect a greater incidence of CKD in the most deprived children, or a faster CKD progression in this population, we believe that they are in themselves further evidence that there is urgent need to develop and validate efficient interventions for families, caregivers, and health professionals to reduce health inequalities in the pediatric CKD population.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods S1. Direct standardization formula for age standardized incidence rate.

Supplementary Methods S2. Multiple imputation method.

Supplementary Table S1. Crude incidence (per 1 million children per year), direct age standardized incidence rates (per 1 million children per year), incidence rate ratios and of kidney replacement therapy according to social deprivation assessed by EDI quintiles (REIN registry 2010–2015).

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