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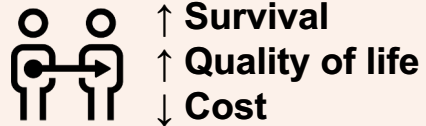


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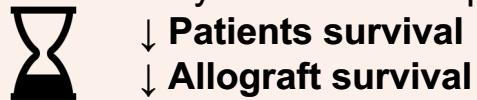
# Social deprivation was directly and indirectly associated with registration on the renal transplantation waiting-list through markers of nephrological care: a mediation analysis.

## Kidney transplantation

Compared with dialysis



Time on dialysis before transplantation



## Low socio-economic status



- ↑ **risk factors of CKD**
- ↑ **severe CKD**
- ↑ **delayed nephrology referral**
- ↑ **emergency start dialysis**

## REIN Registry



**Incident dialysis patients**

N = 16032



**Eligible for registration**

N = 11655



**Registered**

N = 2410

## European Deprivation Index

Least to most deprived national quintiles



13% 14% 16% 21% 36%

**Dialysis patients are frequently deprived**

## Results

### Quintile 5 of the EDI

**Modifiable nephrological care markers**

Emergency start dialysis  
Hb < 11 g/dL and/or lack of EPO  
Albumin < 30 g/L

↓ **Registration**

**Improving predialysis follow-up of the most disadvantaged patients might increase their access to wait-listing**

**Social deprivation reduced registration for kidney transplantation through markers of nephrological care: a mediation analysis**

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## **ABSTRACT**

**Objectives:** We assessed the direct and indirect effect of social deprivation mediated by modifiable markers of nephrological follow-up on registration on the renal transplantation waiting-list.

**Study design and settings:** From the Renal Epidemiology and Information Network, we included French incident dialysis patients eligible for a registration evaluation between January 2017 and June 2018. Mediation analyses were conducted to assess effects of social deprivation estimated by quintile 5 (Q5) of the European Deprivation Index on registration defined as wait-listing at dialysis start or within the first 6 months.

**Results:** Among the 11655 included patients, 2410 were registered. Q5 had a direct effect on registration (OR 0.82 [0.80-0.84]) and an indirect effect mediated by emergency start dialysis (OR 0.97 [0.97-0.98]), hemoglobin < 11 g/dL and/or lack of EPO (OR 0.96 [0.96-0.96]) and albumin < 30 g/L (OR 0.98 [0.98-0.99]).

**Conclusion:** Social deprivation was directly associated with a lower registration on the renal transplantation waiting-list but its effect was also mediated by markers of nephrological care, suggesting that improving the follow-up of the most deprived patients should help to reduce disparities in access to transplantation.

## **KEY WORDS**

Healthcare Disparities, Socioeconomic Factors, Social Deprivation, Kidney transplantation, Mediation Analysis, Renal Insufficiency, Chronic\*/Therapy.

## **RUNNING TITLE**

Social deprivation and access to the renal transplantation waiting-list.

## WHAT IS NEW?

- While there are disparities in access to renal transplantation, data are scarce regarding the association between social deprivation and registration on the waiting-list for renal transplantation in France.
- To better depict causal relationship between social deprivation and registration on the renal transplantation waiting-list, we constructed a directed acyclic graph and performed a mediation analysis.
- Social deprivation estimated by a European ecological index was directly associated with a lower chance of being placed on the renal transplantation waiting-list.
- Starting dialysis in emergency, anemia and hypoalbuminemia, which are some markers of the nephrological follow-up were mediators of the association between social deprivation and registration.
- Improving the follow-up of the most deprived chronic kidney disease patients should be considered an objective for enhancing access to renal transplantation waiting-list.

## INTRODUCTION

In patients with end-stage renal disease (ESRD), it has been established that, compared with dialysis, renal transplantation is associated with a longer survival, a better quality of life, and a lower treatment cost.<sup>1</sup> The time spent on dialysis before transplantation affects both patient and allograft survival<sup>2</sup> and preemptive transplantation is associated with a lower risk of death and a lower likelihood of allograft failure than transplantation performed on dialysis.<sup>3</sup> Thus, the time before registration on the waiting-list is a matter of concern for patients and for nephrologists and is an indicator that could help to implement a quality improvement program.

If early transplantation must be promoted, there is no doubt that there are disparities in access to the waiting-list for renal transplantation across the different countries. In France, Bayat et al.<sup>4</sup> have shown that older age, female gender and region were associated with a lower probability of being registered. In a study from the United Kingdom (UK), ethnicity, smoking status, underlying nephropathy, comorbidities and dialysis modality were associated with the probability of being wait-listed.<sup>5</sup> Couchoud et al.,<sup>6</sup> using a semiparametric cure model, showed that women had a longer duration on dialysis before registration than men. Hogan et al.,<sup>7</sup> in a pediatric cohort of dialysis patients, demonstrated that there was a center effect on the registration on the waiting-list within the first 6 months of dialysis. In a recent study from France, there were variabilities between transplant centers and dialysis networks regarding the odds of registration within the first year of renal replacement therapy (RRT).<sup>8</sup>

To the best of our knowledge, data are scarce and could be discordant regarding the association between social deprivation and registration on the waiting-list for renal transplantation in France, where the healthcare system is universal. In a single-region study, neighborhood deprivation was not associated with placement on the waiting-list<sup>9</sup> whereas one study from our team have shown, through a hierarchical modeling approach, that social deprivation was associated

with lower preemptive registration and that there was variability in preemptive access to the waiting list according to renal unit facilities in North-West France<sup>10</sup>. This last study leads us to think that if social deprivation is associated with early or preemptive registration, this association is not exclusively direct and that it is necessary to study the other potential indirect causal pathways.

The objective of this study was to assess whether SES, estimated by the European Deprivation Index (EDI), was directly associated with placement on the waiting-list for renal transplantation, and if this association could be indirectly explained by markers of nephrological management using a mediation analysis.

## **MATERIALS AND METHODS**

### ***1. Study population and data sources***

This was a retrospective observational multicenter study using data from the Renal Epidemiology and Information Network (REIN) registry. Individuals with ESRD older than 18 years starting dialysis in Metropolitan France who were eligible for an evaluation for a registration on the waiting-list were included. The French recommendation on transplant candidate assessment was implemented at the national level in 2015 to increase the rate of renal transplantation.<sup>11</sup> Contraindications to the initiation of the pretransplant assessment were defined as age > 85, body mass index (BMI) > 50 kg/m<sup>2</sup>, evolutive cancer, oxygen therapy and/or acquired immunodeficiency syndrome (AIDS) of human immunodeficiency virus (HIV) (Figure 1). The study period lasted from 1 January 2017 to 30 June 2018, and the end of the observation was 31 December 2018.

## **2. Study variables**

### *2.1. Event of interest*

Registration was defined as the placement on the waiting-list for a kidney transplant (living or deceased-donor) at dialysis onset or within the first 6 months of RRT. The cut-off at 6 months was chosen *a priori* to reflect rapid registration. Of note, in France, each patient awaiting renal transplantation (with a deceased or with a living-donor) must be registered on the same and unique waiting-list.

### *2.2 Explanatory variable*

The explanatory variable was the European Deprivation Index. The French EDI is constructed from 10 variables: foreign nationality, low level of education, unemployment, unskilled worker, no access to a car, no access to central or electric heating, single-parent family, household  $\geq 6$  people, overcrowded housing, and nonowner. As these variables were both available in the French census data of the National Institute for Statistics and Economic Studies (INSEE) and in the EU-SILC survey (European Union Statistics on Income and Living), it allows comparisons between the countries where it has been validated.<sup>12,13</sup>

The EDI estimates the level of social deprivation of an individual within his structural environment. In France, the EDI is calculated for each smallest geographical unit provided by the INSEE (approximately 2000 inhabitants) and called *Îlot Regroupé pour l'Information Statistique* (IRIS). According to his home address, each patient belongs to an IRIS for which the corresponding EDI is calculated. Thus, the EDI is an ecological proxy of individual social deprivation, for which ecological bias can be considered to be limited given the small size of the geographical unit used.

In our study, the EDI was calculated from the address provided at dialysis initiation and considered as stable over time. It was conventionally divided into national quintiles in the



descriptive analysis, and quintile 5 corresponded to the most deprived patients.<sup>12</sup> As we aimed to study the most deprived patients, the EDI was dichotomized and used as a binary variable (quintile 5 versus the other quintiles) to facilitate mediations analyses.

### *2.3 Patient characteristics*

Characteristics, comorbidities and dialysis characteristics of the incident dialysis patients were collected from the REIN registry.

The following variables were extracted from the original database: age, sex, quintiles of the EDI at dialysis onset, occupational status (active included working and unemployed patients, and inactive included at home, retired and inactive patients), mobility (walking without help and assistance or inability), cardiovascular disease (defined by at least one of this medical history: congestive heart failure, coronary heart disease, dysrhythmia, stroke, transient ischemic attack, peripheral vascular disease and/or abdominal aortic aneurysm), BMI, tobacco use (nonsmoker and former or active smoker), diabetes (type 1 or type 2), chronic respiratory failure (defined by chronic respiratory disease and/or patients with long-term oxygen therapy), underlying nephropathy (polycystic kidney disease (PKD), glomerulonephritis, vascular nephropathy, diabetic nephropathy, pyelonephritis and other or unknown etiology), number of nephrology consultations in the year preceding the initiation of dialysis, initial estimated-glomerular filtration rate (eGFR, CKD-EPI formula), albumin and hemoglobin levels at dialysis onset, dialysis modality (in center hemodialysis, self-care hemodialysis including autodialysis, home hemodialysis and training for home hemodialysis, and peritoneal dialysis (PD)), emergency start and first dialysis on a catheter, and outcomes at 6 months after dialysis onset.

## 2.4 Potential confounders and potential mediators

Potential mediators and confounders were assumed based on the literature data (Supplemental Digital Content). Their presumed relations with quintile 5 of the EDI and with registration are represented in a directed acyclic graph (DAG) (Figure 2).<sup>14</sup>

Potential confounders were age, sex, diabetes, cardiovascular disease, BMI > 30 kg/m<sup>2</sup>, underlying nephropathy and mobility. Mediators were modifiable markers of nephrological management: starting dialysis in emergency, hemoglobin < 11 g/dL and/or lack of EPO, and serum albumin < 30 g/L. Since the study included dialysis patients, we hypothesized that the predialysis care, which include transplantation work up and referral to the transplant center, could affect the early registration.

## 3. Statistical analyses

### 3.1 Univariate, bivariate and multivariable analyses

Characteristics of the complete cohort were described according to the registration status. Categorical data were described by frequencies and percentages. Continuous variables were described by the median and first and third quartiles.

A bivariate analysis using a logistic regression model was performed to evaluate the association between registration on the renal transplantation waiting-list and each variable (Table S5). Regression splines were used to explore the functional form of the continuous variables. As they had no linear relationship with the outcome, BMI, albumin and hemoglobin were dichotomized.

Variables were selected for the multivariable analysis when the p-value was < 0.20 in the bivariate analysis. Sex, age and EDI were included *a priori* in the multivariable analysis. A logistic regression model was used to study the association between patient characteristics and wait-listing.

The interaction between the EDI and sex, age, and diabetes was tested. Multicollinearity has been explored with the variance inflation factor. The uncertainty of the results was expressed with the 95% confidence interval (95% CI).

### *3.2 Missing data*

There were 1342 (11%) missing values for the EDI that were considered missing at random because they were associated with sex, mobility, tobacco, hemoglobin, emergency start and registration. (Table S3). Multiple imputation by chained equation was performed to deal with variable with missing data, and regression coefficients were expressed from the 20 imputed datasets according to Rubin's rules.<sup>15</sup> Table S4 reports patient characteristics from the imputed database. As recommended when an imputation is used for missing data a complete case analysis was performed.

### *3.3 Mediation analyses*

Based on the DAG, a mediation analysis was conducted to estimate to what extent the effect of social deprivation on registration was direct or indirect *via* mediators. A counterfactual approach was used, and the total effect, the natural direct and indirect effects were obtained with an imputed-based approach. Odds ratios (ORs) and 95% CIs were obtained with a nonparametric bootstrap procedure with 1000 samples. Mediators were ordered in the sequential mediation analysis based on the strength of their indirect effect in the "one mediator at a time analysis". The analyses were adjusted for confounders. There was no significant interaction between the exposure and mediators.

### *3.4 Sensitivity analysis*

A sensitivity analysis was performed to assess the robustness of the estimations of direct and indirect effects. According to the VanderWeele method in observational studies, e-values were calculated to estimate how strong a potential unmeasured or residual confounder would have been related to the exposure and the outcome to explain away the observed association.<sup>16</sup> The larger the e-value, the stronger the robustness.

Statistical analyses were performed using R 4.1.0 (R Foundation for Statistical Computing, 2021) with mice and medflex packages.

## **4. Ethical approval**

The REIN registry has the agreement of the French National Ethics Committee “Commission Nationale de l’Informatique et des Libertés” (CNIL). Our study was conducted within the scope of this authorization.

## **RESULTS**

### ***1. Patient characteristics***

Among the 16032 incident dialysis patients during the study period, 11655 patients eligible for a transplant registration assessment were included (Figure 1). Of these, 3686 (36%) belonged to the most deprived national quintile of EDI, 929 (8%) were placed on the transplant waiting-list within the first 6 months of dialysis, and 1481 (13%) were already on the transplant list at dialysis start.

Compared with the other subjects, wait-listed patients were younger (median age 56.3 years vs. 71.5 years), had fewer cardiovascular diseases (616/2410 (26%) vs. 5478/9245 (61%)), were

less frequently diabetic (668/2410 (28%) vs. 4841/9245 (53%)), had less chronic respiratory failure (116/2410 (5%) vs. 1129/9245 (13%)) and had higher median albumin (37.0 [33.0-40.6] vs. 33.5 [29.0-37.7]) and hemoglobin (10.4 [9.4-11.4] vs. 10.0 [8.8-11.0]). The main causes of known underlying nephropathies were glomerulonephritis (495/2410 (21%)) and PKD (466/2410 (19%)) for the registered patients and diabetic nephropathy (2427/9245 (30%)) and vascular nephropathy (2518/9245 (27%)) for the nonregistered subjects. Patients placed on the waiting-list were more often treated by self-care hemodialysis or by PD than their counterparts (468/2410 (19%) vs. 840/9245 (9%) and 437/2410 (18%) vs. 804/9245 (9%), respectively). Wait-listed patients less often started dialysis in emergency than the other subjects (288/2410 (13%) vs. 2680/9245 (30%)). Otherwise, the EDI distribution seemed homogeneous between registered and non-registered patients (quintile 1: 12% vs. 15%; quintile 2: 14% vs. 15%; quintile 3: 16% vs. 19%, quintile 4: 22% vs. 19%; quintile 5: 36% vs. 35%). Patient characteristics are presented in Tables 1, S1 and S2.

## **2. Multivariable analysis**

In the multivariable analysis adjusted for confounders and mediators (Table 2), quintile 5 of the EDI was associated with registration (OR 0.87 [0.77-0.98]). When the mediators were removed from the multivariable analysis, the association between quintile 5 and the registration increased (OR 0.85 [0.75-0.96]). Age at dialysis start (OR 0.94 [0.94-0.95]), male sex (OR 1.19 [1.05-1.34]), nonautonomous mobility (OR 0.24 [0.17-0.35]), underlying nephropathy, diabetes (OR 0.74 [0.63-0.87]), cardiovascular disease (OR 0.51 [0.45-0.58]), BMI > 30 kg/m<sup>2</sup> (OR 0.83 [0.73-0.96]), albumin < 30 g/L (OR 0.58 [0.49-0.69]), hemoglobin < 11 g/dL and/or lack of EPO (OR 0.67 [0.58-0.76]), initiation of dialysis in emergency (OR 0.54 [0.45-0.64]), starting hemodialysis with a catheter (OR 0.42 [0.37-0.48]), self-care hemodialysis (OR 1.33 [1.14-1.55])

and PD (OR 1.65 [1.40-1.94]) were associated with registration on the waiting-list. There was no significant interaction between the EDI and age, sex or diabetes.

### ***3. Mediation analyses***

In the mediation analysis performed with each mediator entered one at a time (Table 3), there was a total effect of quintile 5 on registration on the waiting-list (OR 0.82 [0.80-0.84]). Quintile 5 had a significant indirect effect on wait-listing through emergency start (OR 0.97 [0.97-0.98]), albumin < 30 g/L (OR 0.98 [0.98-0.99]) and hemoglobin < 11 g/dL and/or lack of EPO at dialysis initiation (OR 0.96 [0.96-0.96]).

In the sequential mediation analysis (Table 4), the indirect effect increased slightly when all mediators were entered in the analysis (OR 0.95 [0.94-0.95] to 0.94 [0.94-0.95]).

## **DISCUSSION**

In our study, social deprivation estimated by the EDI was associated with a lower placement on the waiting-list for kidney transplant at the start of dialysis or within the first 6 months of RRT. There was an indirect effect of emergency start, hypoalbuminemia and anemia or lack of EPO at dialysis onset, which are markers of nephrological care. These findings are consistent with the results of previous studies that showed that SES influenced the likelihood of being wait-listed. In the US, employment, insurance coverage and income were associated with registration on the waiting-list before dialysis onset.<sup>17</sup> In Australia, SES had an effect on the registration of young subjects.<sup>18</sup> Low income was associated with decreased wait-listing in Sweden.<sup>19</sup> In the UK, SES estimated by car ownership and housing tenure was associated with registration<sup>20</sup> and access to the transplantation waiting-list was lower for the most deprived quintiles of the Townsend index and

the Carstairs score, especially among older subjects.<sup>21-24</sup> In France, social deprivation measured by the EDI was associated with lower preemptive registration in northwest regions,<sup>10</sup> whereas a single-region study did not find a difference in the likelihood of registration between patients living in deprived or in advantaged neighborhoods.<sup>9</sup>

Previous mediation analyses have been conducted in the field of renal transplantation.<sup>25-28</sup> To the best of our knowledge, our study is the first to focus specifically on the mediators being part of the causal pathway between social deprivation estimated by an ecological index and placement on the renal transplant waiting-list. In our work, starting dialysis in emergency, hemoglobin < 11 g/dL and/or lack of EPO and serum albumin < 30 g/L were associated with registration in the multivariable analysis and were independent mediators of the effect of EDI on wait-listing in the mediation analysis. The OR of the indirect effect was discreetly increased by the successive addition of the mediators in the sequential mediation analysis suggesting an additional effect. These mediators are markers of nephrological care and may reflect the quality of follow-up prior to dialysis onset.<sup>29</sup> Anemia can indicate both a more advanced CKD or a lack of erythropoietin (EPO) treatment. Hypoalbuminemia may suggest poorer control of the underlying glomerulopathy or unaddressed undernutrition. Recent French studies have demonstrated that emergency start of dialysis was associated with social deprivation,<sup>30</sup> hemoglobin < 11 g/dL and serum albumin < 30 g/L,<sup>31</sup> as it is known that an unplanned beginning of dialysis is associated with a lower chance of registration.<sup>32</sup>

Apart from the emergency, nephrology follow-up and predialysis care imply that the patient has already resorted to primary care. It has been demonstrated that SES influenced access and use of healthcare services, even in a universal healthcare system. In the general population, patients with higher incomes were more often on medication, visited specialists and had advanced imaging procedures more often, which may indicate that they had a better follow-up.<sup>33</sup> In a US study, routine

healthcare visits to the practitioner were a mediator of the association between SES and CKD.<sup>34</sup> If the lack of access to primary care leads to a delayed nephrology referral, it may also be influenced by an insufficient knowledge of factors favoring CKD and its progression since it has been shown that SES and education level were associated with delayed referral.<sup>35</sup> As a result, socially deprived patients present more comorbidities<sup>36</sup> and a higher risk of ESRD at presentation to the nephrology department,<sup>37</sup> which would impact the initial care and outcome on dialysis. In a systematic review, Taylor et al.<sup>38</sup> demonstrated that limited health literacy was common in CKD patients, especially in dialysis (27%) compared to transplanted patients (14%) and was associated with a lower educational and socioeconomic status. To be effective in improving care referrals, medical information must be adapted to the level of understanding of patients.

These obstacles may also take part in the pretransplantation evaluation while predialysis care has started, leading to delayed registration on the waiting-list. The completion of medical consultations and laboratory or imaging exams required for the evaluation workup may also be costly for low-SES subjects. Disparities regarding access to required exams for registration have been described according to dialysis facilities type.<sup>39</sup> While it might be complex to understand and to navigate through the healthcare network, navigator programs have been developed.<sup>40</sup>

Finally, it has been shown that access to registration was influenced by a center effect, suggesting variability of practices.<sup>4,7,8</sup> Our study showed that patients treated with PD and self-care hemodialysis were wait-listed earlier than those who received in-center hemodialysis. It is possible that, depending on the level of education and understanding and on the housing conditions of the most deprived patients, the physician differently managed predialysis care and modality dialysis offerings. This hypothesis is particularly based on a recent study by our team that demonstrated that social deprivation was associated with lower PD uptake in a direct manner but also in an indirect way through a proxy of predialysis care.<sup>41</sup>



The strength of this study rested on its large population, stemming from the national REIN registry where the data of all patients treated by RRT in France are collected. However, our study has limitations. Given the collection methods of the registry, there may be a declarative bias and the exact dates of hemoglobin and albumin measurement at dialysis onset were not available. The EDI was calculated from the address at dialysis onset and was considered stable over time, which may constitute a temporality bias especially for patients preemptively registered. Moves, IRIS and EDI changes have not been taken into account. Unfortunately, some data that would allow us to better appreciate the nephrological follow-up were unavailable in our database – such as the number of consultations with the general practitioner or the attempt to create an arteriovenous fistula – or uninterpretable, such as the number of nephrology consultations before dialysis onset that had too much missing data to be analyzed (41%). The measure of the association between the EDI and registration may have been affected by residual confounders and mediators not collected in the database. The calculated e-values of the OR were all greater than 1 but remained below 1.6, which means that an unmeasured confounder with an OR of 1.6 on the exposure and on the outcome could fully explain the results. Finally, as the EDI is a composite index, variables included in the EDI calculation could be considered possible mediators reflecting geographic isolation (no access to a car) or weak health literacy level (unskilled or farm-worker, unemployment, low level of education defined as less than first stage of secondary-level education).

In our study, the direct effect of quintile 5 of the EDI on wait-listing remained significant in the different models of mediation analyses, suggesting that other causal pathways may explain the effect of social deprivation on registration. Geographical remoteness could be associated with social deprivation and could partly explain its effect on access to care.<sup>42,43</sup> In two studies from France and the US, distance to center was not associated with early registration.<sup>4,44</sup> In the US, patients living in rural areas were less often registered on the kidney transplantation waiting-list

than those living in urban areas,<sup>45</sup> whereas a Scottish and a Canadian studies found that wait-listing for kidney transplantation was faster for patients living far from the transplant center.<sup>21,46</sup>

In conclusion, our study demonstrated that despite universal healthcare coverage, social deprivation was frequent and restrained registration on the renal transplantation waiting-list, partly through markers of nephrological management. Improving the nephrological follow-up of the most disadvantaged patients is consequently a subject of interest. Further studies are needed to explore the role of other mediators between SES and placement on the waiting-list, such as health literacy, geographic remoteness and health accessibility<sup>43</sup>.

## **ETHICS APPROVAL**

The REIN registry has the agreement of the French National Ethics Committee “Commission Nationale de l’Informatique et des Libertés” (CNIL). Our study was conducted within the scope of this authorization.

## **AUTHORS' CONTRIBUTIONS**

All authors contributed to research design and implementation. *EC* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper. *LL* performed the EDI calculation. *SB* and *MB* participated in the proofreading of the manuscript. *ML* and *CC* collected data. *TL* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper. *VC* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper.

## **DATA AVAILABILITY**

Data supporting the findings of this study are available from the corresponding author on reasonable request.

## **SUPPLEMENTARY DATA**

Supplementary data are available at *IJE* online.

## **FUNDING**

The study was funded by a grant from the 'Agence de la Biomédecine'.

## **CONFLICT OF INTEREST**

None declared.

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## TABLES

**Table 1.** Patient characteristics according to their registration status.

	<b>Complete cohort</b> N=11655	<b>Not registered</b> N=9245	<b>Registered</b> N=2410
<b>Age</b>	69.0 [57.7-77.3]	71.5 [62.7-78.9]	56.3 [46.4-66.0]
<b>Sex</b>			
Female	4243 (36%)	3357 (36%)	886 (37%)
Male	7412 (64%)	5888 (64%)	1524 (63%)
<b>National quintile of the EDI</b>			
Quintile 1	1310 (13%)	974 (12%)	336 (15%)
Quintile 2	1492 (14%)	1138 (14%)	354 (15%)
Quintile 3	1642 (16%)	1281 (16%)	361 (19%)
Quintile 4	2183 (21%)	1755 (22%)	428 (19%)
Quintile 5	3686 (36%)	2874 (36%)	812 (35%)
<b>Cardiovascular disease</b>	6094 (54%)	5478 (61%)	616 (26%)
<b>BMI <math>\leq</math> 30 kg/m<sup>2</sup></b>	7465 (74%)	5854 (73%)	1611 (79%)
<b>Tobacco</b>			
Non smoker	5482 (55%)	4250 (55%)	1232 (58%)
Former or active smoker	4396 (45%)	3511 (45%)	885 (42%)
<b>Diabetes</b>	5509 (48%)	4841 (53%)	668 (28%)
<b>Chronic respiratory failure</b>	1245 (11%)	1129 (13%)	116 (5%)
<b>Underlying nephropathy</b>			
PKD	798 (7%)	332 (4%)	466 (19%)
Glomerulonephritis	1346 (12%)	851 (9%)	495 (21%)
Vascular	2914 (25%)	2518 (27%)	396 (16%)
Diabetic	2814 (24%)	2427 (30%)	387 (16%)
Pyelonephritis	464 (4%)	373 (4%)	91 (4%)
Other/Unknown	3319 (28%)	2744 (30%)	575 (24%)
<b>eGFR, mL/min/1.73 m<sup>2</sup></b>	8.00 [5.94-10.53]	8.14 [6.01-10.79]	7.48 [5.75-9.64]
<b>Albumin</b>			
Continuous variable	34.0 [29.8-38.2]	33.5 [29.0-37.7]	37.0 [33.0-40.6]
< 30 g/L	2131 (25%)	1896 (28%)	236 (13%)
<b>Hemoglobin</b>			
Continuous variable	10.0 [8.9-11.1]	10.0 [8.8-11.0]	10.4 [9.4-11.4]
< 11 g/dL	7507 (72%)	6121 (74%)	1386 (65%)
<b>EPO at dialysis start</b>	4696 (46%)	3597 (45%)	1099 (53%)
<b>Dialysis modality</b>			
In center hemodialysis	9106 (78%)	7601 (82%)	1505 (62%)
Self-care hemodialysis	1308 (11%)	840 (9%)	468 (19%)
Peritoneal dialysis	1241 (11%)	804 (9%)	437 (18%)
<b>Emergency start</b>	2968 (27%)	2680 (30%)	288 (13%)
<b>Start on a catheter</b>	5671 (53%)	5033 (58%)	638 (30%)

*Continuous variables are described by median and [interquartile range] and categorical variables are described by frequencies and (percentage).*

*EDI: European Deprivation Index; BMI: body mass index; PKD: polycystic kidney disease; eGFR: estimated glomerular filtration rate (CKD-EPI formula).*

**Table 2.** Multivariable analysis. Factors associated with registration.

	<b>Model without mediators</b>	<b>Model with mediators</b>
	OR [95% CI]	OR [95% CI]
<b>Patient characteristics and comorbidities</b>		
<b>Age</b>	0.95 [0.94-0.95]*	0.94 [0.94-0.95]*
<b>Sex</b>		
Female	ref	ref
Male	1.18 [1.05-1.33]*	1.19 [1.05-1.34]*
<b>Quintile of the EDI</b>		
Other quintiles	ref	ref
Quintile 5	0.85 [0.75-0.96]*	0.87 [0.77-0.98]*
<b>Mobility</b>		
Without help	ref	ref
Assistance or inability	0.23 [0.16-0.32]*	0.24 [0.17-0.35]*
<b>Cardiovascular disease</b>	0.49 [0.43-0.56]*	0.51 [0.45-0.58]*
<b>BMI</b>		
≤ 30 kg/m <sup>2</sup>	ref	ref
> 30 kg/m <sup>2</sup>	0.87 [0.75-0.99]*	0.83 [0.73-0.96]*
<b>Tobacco</b>		
Non smoker	ref	ref
Former or active smoker	1.00 [0.88-1.13]	0.99 [0.87-1.12]
<b>Diabetes</b>	0.73 [0.62-0.85]*	0.74 [0.63-0.87]*
<b>Chronic respiratory failure</b>	0.76 [0.61-0.95]*	0.79 [0.63-0.98]*
<b>Underlying nephropathy</b>		
PKD	ref	ref
Glomerulonephritis	0.47 [0.38-0.58]*	0.52 [0.42-0.64]*
Vascular	0.29 [0.24-0.36]*	0.32 [0.26-0.40]*
Diabetic	0.36 [0.28-0.46]*	0.40 [0.31-0.51]*
Pyelonephritis	0.25 [0.18-0.34]*	0.26 [0.19-0.36]*
Other/Unknown	0.28 [0.23-0.35]*	0.31 [0.26-0.38]*
<b>Biological characteristics</b>		
<b>Albumin</b>		
< 30 g/L	-	0.58 [0.49-0.69]*
≥ 30 g/L	-	ref
<b>Anemia</b>		
< 11 g/dL and/or lack of EPO	-	0.67 [0.58-0.76]*
≥ 11 g/dL and/or EPO	-	ref
<b>Dialysis characteristics</b>		
<b>Dialysis modality</b>		
In center hemodialysis	ref	ref
Self-care hemodialysis	1.38 [1.18-1.60]*	1.33 [1.14-1.55]*
Peritoneal dialysis	1.89 [1.61-2.22]*	1.65 [1.40-1.94]*
<b>Emergency start</b>	-	0.54 [0.45-0.64]*
<b>Start on a catheter</b>	0.29 [0.26-0.33]*	0.42 [0.37-0.48]*

OR: odds ratio; CI: confidence interval; EDI: European Deprivation Index; BMI: body mass index; PKD: polycystic kidney disease.

\* p < 0.05

**Table 3.** Mediation analysis. Effects of social deprivation on registration.

	<b>Emergency start</b>	<b>Serum albumin &lt; 30 g/L</b>	<b>Hemoglobin &lt; 11 g/dL and/or lack of EPO</b>
	OR [95% CI]	OR [95% CI]	OR [95% CI]
<b>Natural Direct Effect</b>	0.84 [0.82-0.87]**	0.83 [0.81-0.85]**	0.86 [0.84-0.88]**
<b>Natural Indirect Effect</b>	0.97 [0.97-0.98]**	0.98 [0.98-0.99]**	0.96 [0.96-0.96]**
<b>Total Effect</b>	0.82 [0.80-0.84]**	0.82 [0.80-0.84]**	0.82 [0.80-0.84]**

The analyses were adjusted for confounders: age, sex, diabetes, underlying nephropathy, cardiovascular disease, BMI > 30 kg/m<sup>2</sup> and mobility.

*EPO: erythropoietin, BMI: body mass index.*

\*\* p < 0.001

**Table 4.** Sequential mediation analysis. Effects of social deprivation on registration.

	<b>Hemoglobin &lt; 11 g/dL and/or lack of EPO</b>	<b>Hemoglobin &lt; 11 g/dL and/or lack of EPO + Emergency start</b>	<b>Hemoglobin &lt; 11 g/dL and/or lack of EPO + Emergency start + Albumin &lt; 30 g/L</b>
	OR [95% CI]	OR [95% CI]	OR [95% CI]
<b>Natural Direct Effect</b>	0.87 [0.85-0.89]**	0.87 [0.85-0.89]**	0.87 [0.85-0.89]**
<i>e-value</i>	1.35	1.35	1.35
<b>Natural Indirect Effect</b>	0.95 [0.94-0.95]**	0.95 [0.94-0.95]**	0.94 [0.94-0.95]**
<i>e-value</i>	1.19	1.21	1.21
<b>Total Effect</b>	0.82 [0.80-0.84]**	0.82 [0.80-0.84]**	0.82 [0.80-0.84]**
<i>e-value</i>	1.44	1.44	1.44

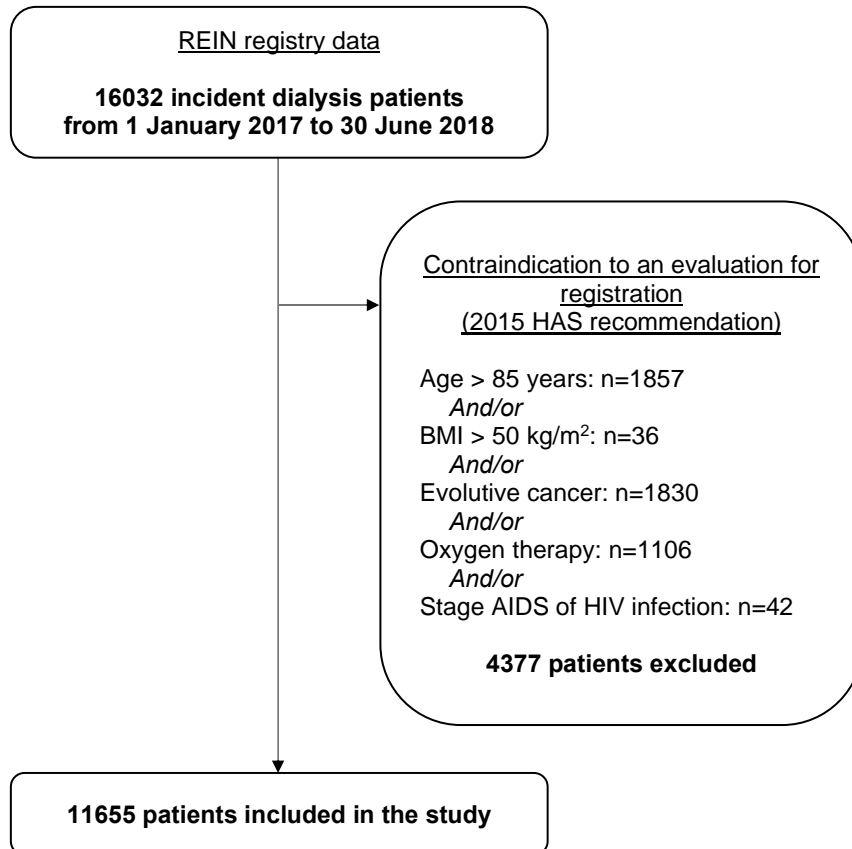
The analyses were adjusted for confounders: age, sex, diabetes, underlying nephropathy, cardiovascular disease, BMI > 30 kg/m<sup>2</sup> and mobility.

*EPO*: erythropoietin, *BMI*: body mass index.

\*\* p < 0.001

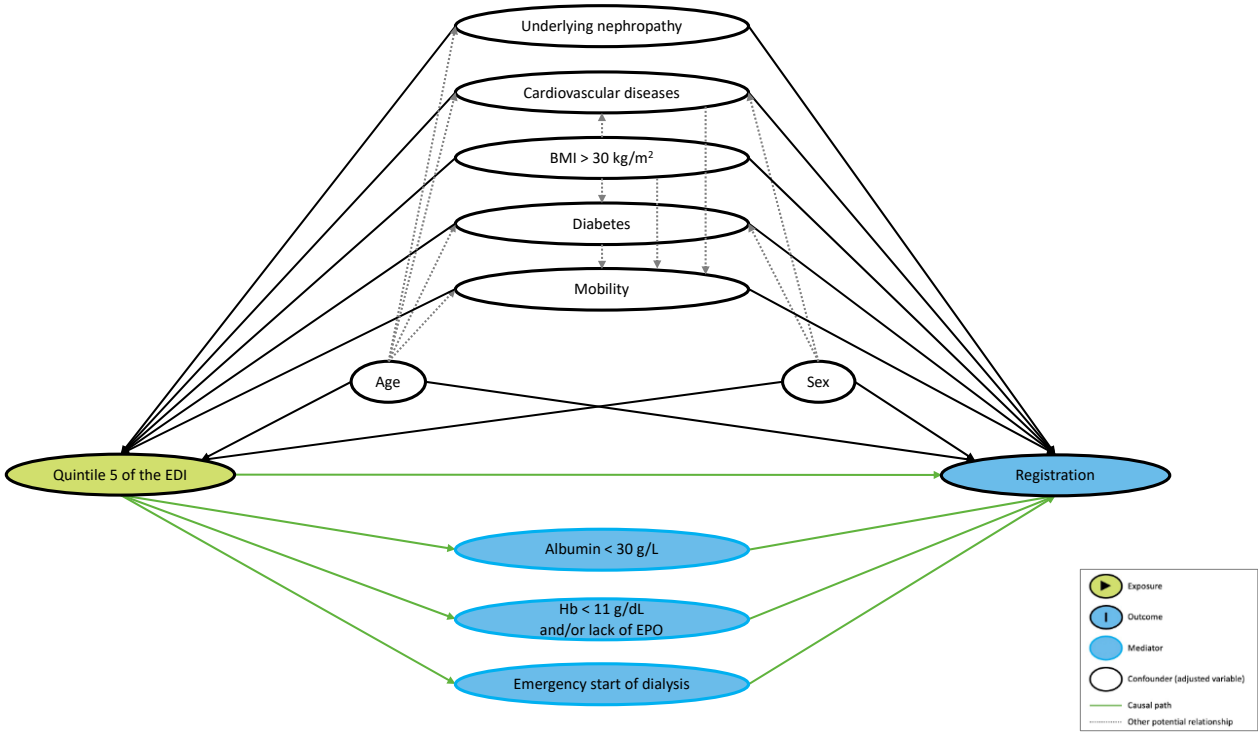
## FIGURES

**Figure 1.** Flow chart of the study.



*REIN: Renal Epidemiology and Information Network; HAS: Haute Autorité de Santé; BMI: body mass index; AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus.*

**Figure 2.** Directed acyclic graph.



Causal assumptions in the relationship between social deprivation and registration on the renal transplantation waiting-list, with potential confounders and potential mediators.

*EDI: European Deprivation Index; BMI: body mass index; Hb: hemoglobin, EPO: erythropoietin.*

### **Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



## **WHAT IS NEW ?**

- While there are disparities in access to renal transplantation, data are scarce regarding the association between social deprivation and registration on the waiting-list for renal transplantation in France.
- To better depict causal relationship between social deprivation and registration on the renal transplantation waiting-list, we constructed a directed acyclic graph and performed a mediation analysis.
- Social deprivation estimated by a European ecological index was directly associated with a lower chance of being placed on the renal transplantation waiting-list.
- Starting dialysis in emergency, anemia and hypoalbuminemia, which are some markers of the nephrological follow-up were mediators of the association between social deprivation and registration.
- Improving the follow-up of the most deprived chronic kidney disease patients should be considered an objective for enhancing access to renal transplantation waiting-list.

## **AUTHOR STATEMENT**

All authors contributed to research design and implementation. *EC* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper. *LL* performed the EDI calculation. *SB* and *MB* participated in the proofreading of the manuscript. *ML* and *CC* collected data. *TL* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper. *VC* participated in the research design, in the performance of the research, in data analysis and in the writing of the paper.