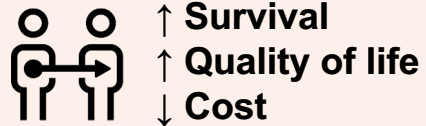


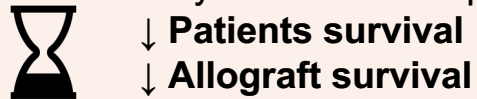
Social deprivation was directly and indirectly associated with registration on the renal transplantation waiting-list through markers of nephrological care: a mediation analysis.

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

Eve Calvar, MD*^{1,2,3}, *Ludivine Launay*, MSc², *Sahar Bayat-Makoei*, MD,PhD⁴, *Marc Bauwens*, MD⁵, *Mathilde Lassalle*, MSc⁶, *Cécile Couchoud*, MD,PhD⁶, *Thierry Lobbedez*, MD^{1,2,3,7} and *Valérie Châtelet*, MD,PhD^{1,2,3}

¹Centre Universitaire des Maladies Rénales, Centre Hospitalier Universitaire de Caen, 14033 Caen Cedex 09, France

²U1086 INSERM, Centre de Lutte Contre le Cancer François Baclesse, BP 45026, 14076 Caen Cedex 05, France

³Université Caen Normandie – UFR de médecine (Medical School), 2 Rue des Rochambelles, 14032 Caen Cedex 5, France

⁴Univ Rennes, Ecole des Hautes Etudes en Santé Publique (EHESP), Recherche en pharmaco-épidémiologie et recours aux soins (REPERES) – EA 7449, 15 Avenue du Professeur Léon Bernard, 35043 Rennes, France

⁵Department of Nephrology Hemodialysis, Poitiers University Hospital, Poitiers, France

⁶REIN Registry, Biomedecine Agency, France

⁷RDPLF, 30 rue Sere Depoin, 95300 Pontoise, France

***Corresponding author**

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.¹ The time spent on dialysis before transplantation affects both patient and allograft survival² and preemptive transplantation is associated with a lower risk of death and a lower likelihood of allograft failure than transplantation performed on dialysis.³ 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.⁴ 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.⁵ Couchoud et al.,⁶ using a semiparametric cure model, showed that women had a longer duration on dialysis before registration than men. Hogan et al.,⁷ 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).⁸

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-list⁹ 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 France¹⁰. 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.¹¹ Contraindications to the initiation of the pretransplant assessment were defined as age > 85, body mass index (BMI) > 50 kg/m², 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 ≥ 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.^{12,13}

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.¹² 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).¹⁴

Potential confounders were age, sex, diabetes, cardiovascular disease, BMI > 30 kg/m², 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.¹⁵ 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.¹⁶ 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/m² (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.¹⁷ In Australia, SES had an effect on the registration of young subjects.¹⁸ Low income was associated with decreased wait-listing in Sweden.¹⁹ In the UK, SES estimated by car ownership and housing tenure was associated with registration²⁰ 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.²¹⁻²⁴ In France, social deprivation measured by the EDI was associated with lower preemptive registration in northwest regions,¹⁰ whereas a single-region study did not find a difference in the likelihood of registration between patients living in deprived or in advantaged neighborhoods.⁹

Previous mediation analyses have been conducted in the field of renal transplantation.²⁵⁻²⁸ 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.²⁹ 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,³⁰ hemoglobin < 11 g/dL and serum albumin < 30 g/L,³¹ as it is known that an unplanned beginning of dialysis is associated with a lower chance of registration.³²

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.³³ In a US study, routine

healthcare visits to the practitioner were a mediator of the association between SES and CKD.³⁴ 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.³⁵ As a result, socially deprived patients present more comorbidities³⁶ and a higher risk of ESRD at presentation to the nephrology department,³⁷ which would impact the initial care and outcome on dialysis. In a systematic review, Taylor et al.³⁸ 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.³⁹ While it might be complex to understand and to navigate through the healthcare network, navigator programs have been developed.⁴⁰

Finally, it has been shown that access to registration was influenced by a center effect, suggesting variability of practices.^{4,7,8} 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.⁴¹

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.^{42,43} In two studies from France and the US, distance to center was not associated with early registration.^{4,44} In the US, patients living in rural areas were less often registered on the kidney transplantation waiting-list

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

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 accessibility⁴³.

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

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant.* 2011;11:2093-2109.
2. Haller MC, Kammer M, Oberbauer R. Dialysis vintage and outcomes in renal transplantation. *Nephrol Dial Transplant.* 2019;34:555-560.
3. Abramowicz D, Hazzan M, Maggiore U, et al. Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP. *Nephrol Dial Transplant.* 2016;31:691-697.
4. Bayat S, Frimat L, Thilly N, Loos C, Briançon S, Kessler M. Medical and non-medical determinants of access to renal transplant waiting list in a French community-based network of care. *Nephrol Dial Transplant.* 2006;21:2900-2907.
5. Akolekar D, Forsythe JL, Oniscu GC. Impact of patient characteristics and comorbidity profile on activation of patients on the kidney transplantation waiting list. *Transplant Proc.* 2013;45:2115-2122.
6. Couchoud C, Bayat S, Villar E, Jacquelinet C, Ecochard R. A new approach for measuring gender disparity in access to renal transplantation waiting lists. *Transplantation.* 2012;94:513-519.
7. Hogan J, Savoye E, Macher MA, et al. Rapid access to renal transplant waiting list in children: impact of patient and centre characteristics in France. *Nephrol Dial Transplant.* 2014;29:1973-1979.
8. Couchoud C, Bayer F, Rabilloud M, et al. Effect of age and care organization on sources of variation in kidney transplant waiting list registration. *Am J Transplant.* 2021;21:3608-3617.

9. Kihal-Talantikite W, Vigneau C, Deguen S, Siebert M, Couchoud C, Bayat S. Influence of socio-economic inequalities on access to renal transplantation and survival of patients with end-stage renal disease. *PLoS One*. 2016;11:e0153431.
10. Riffaut N, Lobbedez T, Hazzan M, et al. Access to preemptive registration on the waiting list for renal transplantation: a hierarchical modeling approach. *Transpl Int*. 2015;28:1066-1073.
11. Transplantation Rénale - Accès à la Liste d'Attente Nationale. https://www.has-sante.fr/jcms/c_1751188/fr/transplantation-renale-acces-a-la-liste-d-attente-nationale. Published December 2, 2015. Accessed September 19, 2021.
12. Pernet C, Delpierre C, Dejardin O, et al. Construction of an adaptable European transnational ecological deprivation index: the French version. *J Epidemiol Community Health*. 2012;66:982-989.
13. Guillaume E, Pernet C, Dejardin O, et al. Development of a cross-cultural deprivation index in five European countries. *J Epidemiol Community Health*. 2016;70:493-499.
14. Tennant PWG, Murray EJ, Arnold KF, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. *Int J Epidemiol*. 2021;50:620-632.
15. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons Inc.; 1987.
16. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268-274.
17. Kasiske BL, London W, Ellison MD. Race and socioeconomic factors influencing early placement on the kidney transplant waiting list. *J Am Soc Nephrol*. 1998;9:2142-2147.
18. Sypek MP, Clayton PA, Lim W, et al. Access to waitlisting for deceased donor kidney transplantation in Australia. *Nephrology (Carlton)*. 2019;24:758-766.

19. Zhang Y, Gerdtham UG, Rydell H, Jarl J. Socioeconomic inequalities in the kidney transplantation process: a registry-based study in Sweden. *Transplant Direct*. 2018;4:e346.
20. Pruthi R, Robb ML, Oniscu GC, et al. Inequity in access to transplantation in the United Kingdom. *Clin J Am Soc Nephrol*. 2020;15:830-842.
21. Dudley CR, Johnson RJ, Thomas HL, Ramanan R, Ansell D. Factors that influence access to the national renal transplant waiting list. *Transplantation*. 2009;88:96-102.
22. Udayaraj U, Ben-Shlomo Y, Roderick P, et al. Social deprivation, ethnicity, and access to the deceased donor kidney transplant waiting list in England and Wales. *Transplantation*. 2010;90:279-285.
23. Oniscu GC, Schalkwijk AA, Johnson RJ, Brown H, Forsythe JL. Equity of access to renal transplant waiting list and renal transplantation in Scotland: cohort study. *Bmj*. 2003;327:1261.
24. Caskey FJ. Renal replacement therapy: can we separate the effects of social deprivation and ethnicity? *Kidney Int Suppl (2011)*. 2013;3:246-249.
25. Driollet B, Bayer F, Chatelet V, et al. Social deprivation is associated with poor kidney transplantation outcome in children. *Kidney Int*. 2019;96:769-776.
26. Bailey PK, Caskey FJ, MacNeill S, Tomson CRV, Dor F, Ben-Shlomo Y. Mediators of socioeconomic inequity in living-donor kidney transplantation: results from a UK multicenter case-control study. *Transplant Direct*. 2020;6:e540.
27. Murphy KA, Jackson JW, Purnell TS, et al. Association of socioeconomic status and comorbidities with racial disparities during kidney transplant evaluation. *Clin J Am Soc Nephrol*. 2020;15:843-851.

28. Calvar E, Launay L, Boyer A, Launoy G, Lobbedez T, Châtelet V. Effects of social deprivation on the proportion of preemptive kidney transplantation: a mediation analysis. *Transplant Direct*. 2021;7:e750.
29. CKD Evaluation and Management – KDIGO. <https://kdigo.org/guidelines/ckd-evaluation-and-management/>. Published July 13, 2013. Accessed September 20, 2021.
30. Beaumier M, Béchade C, Dejardin O, et al. Is self-care dialysis associated with social deprivation in a universal health care system? A cohort study with data from the renal epidemiology and information network registry. *Nephrol Dial Transplant*. 2020;35:861-869.
31. Raffray M, Vigneau C, Couchoud C, Bayat S. Predialysis care trajectories of patients with ESKD starting dialysis in emergency in France. *Kidney Int Rep*. 2021;6:156-167.
32. Pladys A, Morival C, Couchoud C, et al. Outcome-dependent geographic and individual variations in the access to renal transplantation in incident dialysed patients: a French nationwide cohort study. *Transpl Int*. 2019;32:369-386.
33. Filc D, Davidovich N, Novack L, Balicer RD. Is socioeconomic status associated with utilization of health care services in a single-payer universal health care system? *Int J Equity Health*. 2014;13:115.
34. Vart P, Gansevoort RT, Crews DC, Reijneveld SA, Bültmann U. Mediators of the association between low socioeconomic status and chronic kidney disease in the United States. *Am J Epidemiol*. 2015;181:385-396.
35. Navaneethan SD, Aloudat S, Singh S. A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease. *BMC Nephrol*. 2008;9:3.

36. Pathirana TI, Jackson CA. Socioeconomic status and multimorbidity: a systematic review and meta-analysis. *Aust N Z J Public Health*. 2018;42:186-194.
37. Bello AK, Peters J, Rigby J, Rahman AA, El Nahas M. Socioeconomic status and chronic kidney disease at presentation to a renal service in the United Kingdom. *Clin J Am Soc Nephrol*. 2008;3:1316-1323.
38. Taylor DM, Fraser SDS, Bradley JA, et al. A systematic review of the prevalence and associations of limited health literacy in CKD. *Clin J Am Soc Nephrol*. 2017;12:1070-1084.
39. Garg PP, Frick KD, Diener-West M, Powe NR. Effect of the ownership of dialysis facilities on patients' survival and referral for transplantation. *N Engl J Med*. 1999;341:1653-1660.
40. Sullivan C, Leon JB, Sayre SS, et al. Impact of navigators on completion of steps in the kidney transplant process: a randomized, controlled trial. *Clin J Am Soc Nephrol*. 2012;7:1639-1645.
41. Beaumier M, Calvar E, Launay L, et al. Effect of social deprivation on peritoneal dialysis uptake: a mediation analysis with the data of the REIN registry. *Perit Dial Int*. 2021. doi: 10.1177/08968608211023268.
42. Wang F, Luo W. Assessing spatial and nonspatial factors for healthcare access: towards an integrated approach to defining health professional shortage areas. *Health Place*. 2005;11:131-146.
43. Launay L, Guillot F, Gaillard D, et al. Methodology for building a geographical accessibility health index throughout metropolitan France. *PLoS One*. 2019;14:e0221417.
44. Patzer RE, Amaral S, Wasse H, Volkova N, Kleinbaum D, McClellan WM. Neighborhood poverty and racial disparities in kidney transplant waitlisting. *J Am Soc Nephrol*. 2009;20:1333-1340.

45. Axelrod DA, Guidinger MK, Finlayson S, et al. Rates of solid-organ wait-listing, transplantation, and survival among residents of rural and urban areas. *JAMA*. 2008;299:202-207.
46. Tonelli M, Klarenbach S, Rose C, Wiebe N, Gill J. Access to kidney transplantation among remote- and rural-dwelling patients with kidney failure in the United States. *JAMA*. 2009;301:1681-1690.

TABLES

Table 1. Patient characteristics according to their registration status.

	Complete cohort N=11655	Not registered N=9245	Registered N=2410
Age	69.0 [57.7-77.3]	71.5 [62.7-78.9]	56.3 [46.4-66.0]
Sex			
Female	4243 (36%)	3357 (36%)	886 (37%)
Male	7412 (64%)	5888 (64%)	1524 (63%)
National quintile of the EDI			
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%)
Cardiovascular disease	6094 (54%)	5478 (61%)	616 (26%)
BMI \leq 30 kg/m²	7465 (74%)	5854 (73%)	1611 (79%)
Tobacco			
Non smoker	5482 (55%)	4250 (55%)	1232 (58%)
Former or active smoker	4396 (45%)	3511 (45%)	885 (42%)
Diabetes	5509 (48%)	4841 (53%)	668 (28%)
Chronic respiratory failure	1245 (11%)	1129 (13%)	116 (5%)
Underlying nephropathy			
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%)
eGFR, mL/min/1.73 m²	8.00 [5.94-10.53]	8.14 [6.01-10.79]	7.48 [5.75-9.64]
Albumin			
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%)
Hemoglobin			
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%)
EPO at dialysis start	4696 (46%)	3597 (45%)	1099 (53%)
Dialysis modality			
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%)
Emergency start	2968 (27%)	2680 (30%)	288 (13%)
Start on a catheter	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.

	Model without mediators	Model with mediators
	OR [95% CI]	OR [95% CI]
Patient characteristics and comorbidities		
Age	0.95 [0.94-0.95]*	0.94 [0.94-0.95]*
Sex		
Female	ref	ref
Male	1.18 [1.05-1.33]*	1.19 [1.05-1.34]*
Quintile of the EDI		
Other quintiles	ref	ref
Quintile 5	0.85 [0.75-0.96]*	0.87 [0.77-0.98]*
Mobility		
Without help	ref	ref
Assistance or inability	0.23 [0.16-0.32]*	0.24 [0.17-0.35]*
Cardiovascular disease	0.49 [0.43-0.56]*	0.51 [0.45-0.58]*
BMI		
≤ 30 kg/m ²	ref	ref
> 30 kg/m ²	0.87 [0.75-0.99]*	0.83 [0.73-0.96]*
Tobacco		
Non smoker	ref	ref
Former or active smoker	1.00 [0.88-1.13]	0.99 [0.87-1.12]
Diabetes	0.73 [0.62-0.85]*	0.74 [0.63-0.87]*
Chronic respiratory failure	0.76 [0.61-0.95]*	0.79 [0.63-0.98]*
Underlying nephropathy		
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]*
Biological characteristics		
Albumin		
< 30 g/L	-	0.58 [0.49-0.69]*
≥ 30 g/L	-	ref
Anemia		
< 11 g/dL and/or lack of EPO	-	0.67 [0.58-0.76]*
≥ 11 g/dL and/or EPO	-	ref
Dialysis characteristics		
Dialysis modality		
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]*
Emergency start	-	0.54 [0.45-0.64]*
Start on a catheter	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.

	Emergency start	Serum albumin < 30 g/L	Hemoglobin < 11 g/dL and/or lack of EPO
	OR [95% CI]	OR [95% CI]	OR [95% CI]
Natural Direct Effect	0.84 [0.82-0.87]**	0.83 [0.81-0.85]**	0.86 [0.84-0.88]**
Natural Indirect Effect	0.97 [0.97-0.98]**	0.98 [0.98-0.99]**	0.96 [0.96-0.96]**
Total Effect	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/m² and mobility.

EPO: erythropoietin, BMI: body mass index.

** p < 0.001

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

	Hemoglobin < 11 g/dL and/or lack of EPO	Hemoglobin < 11 g/dL and/or lack of EPO + Emergency start	Hemoglobin < 11 g/dL and/or lack of EPO + Emergency start + Albumin < 30 g/L
	OR [95% CI]	OR [95% CI]	OR [95% CI]
Natural Direct Effect	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
Natural Indirect Effect	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
Total Effect	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

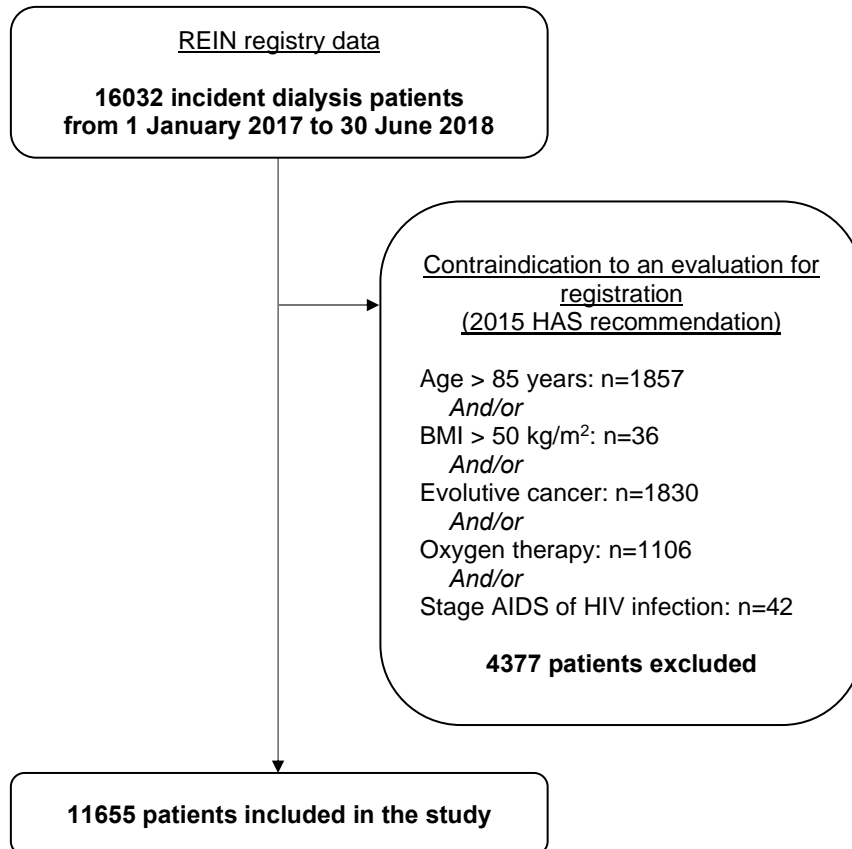
The analyses were adjusted for confounders: age, sex, diabetes, underlying nephropathy, cardiovascular disease, BMI > 30 kg/m² and mobility.

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

** p < 0.001

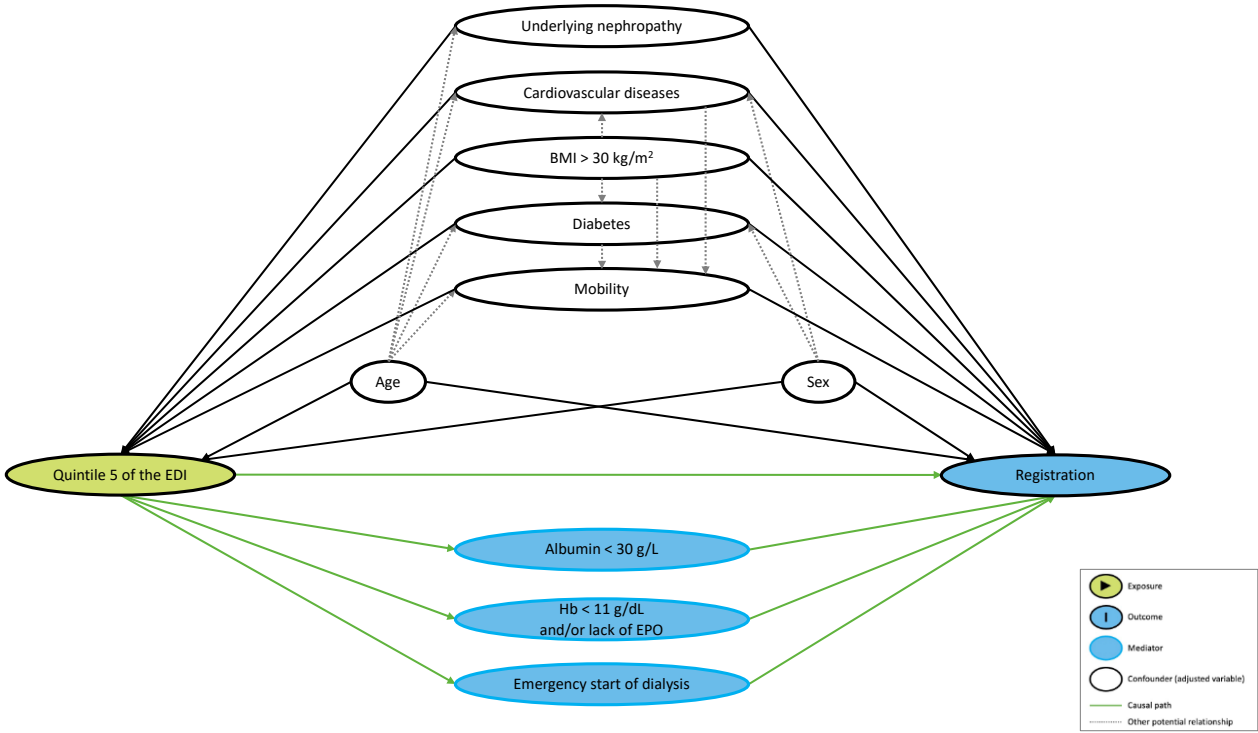
FIGURES

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.