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Effects of Social Deprivation on the Proportion of Preemptive Kidney Transplantation: A Mediation Analysis

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Background. Social inequalities in health lead to an increased risk of chronic kidney disease and less access to renal transplantation. The objective of this study was to assess the association between social deprivation estimated by the fifth quintile of the European Deprivation Index (EDI) and preemptive kidney transplantation (PKT) and to explore the potential mediators of this association. **Methods.** This retrospective observational multicenter study included 8701 patients who received their first renal transplant in France between 2010 and 2014. Mediation analyses were performed to assess the direct and indirect effects of the EDI on PKT. **Results.** Among the 8701 transplant recipients, 32.4% belonged to the most deprived quintile of the EDI (quintile 5) and 16% received a PKT (performed either with a deceased- or living-donor). There was a significant association between quintile 5 of the EDI and PKT (total effect: odds ratio [OR]: 0.64 [95% confidence interval (CI): 0.55-0.73]). Living-donor kidney transplantation was the main mediator of this association (natural indirect effect: OR: 0.92 [0.89–0.95]). To a lesser extent, positive cytomegalovirus and hepatitis C serologies and blood group B were also mediators (respective natural indirect effects: OR: 0.98 [95% CI: 0.95-1.00], OR: 0.99 [95% CI: 0.99-1.00], and OR: 0.99 [95% CI: 0.98-1.00], $P < 0.05$). **Conclusions.** Our study suggests that social deprivation is associated with a decreased proportion of PKT. This association might be mitigated by promoting living-donor transplantation.

It is widely accepted that, compared with dialysis, renal transplantation is associated with a lower risk of mortality and a greater quality of life.[1] Large-scale studies have demonstrated that patients transplanted before beginning dialysis had a lower risk of death than subjects who were transplanted while on dialysis.[2,3] Furthermore, it has been shown that the time spent on dialysis before transplantation affects patient survival.[3] The beneficial effect of preemptive transplantation on renal allograft survival is more controversial.[4] Nevertheless, longer transplant survival was found when transplantation was performed from a living donor[5-7] and when living-donor transplantation was performed preemptively rather than after the initiation of dialysis.[7] Recent recommendations encourage preemptive living-donor kidney transplantation (LDKT).[8]

On the other hand, it has been demonstrated that there are social inequalities in access to preemptive renal transplantation.[9-11] In France, it has been suggested that social deprivation could influence access to preemptive registration.[12] There is a lack of data regarding the underlying mechanism by which social deprivation affects preemptive renal transplantation. Decreased access to living-donor transplantation of the most deprived population may partially explain this social inequity.[9,10,13]

The European Deprivation Index (EDI) is a composite index that measures social deprivation. It contains variables common, on the one hand, to the European Union Statistics on Income and Living survey that studied objective poverty and the concept of individual perception of needs called "subjective poverty" in 26 European countries[14] and, on the other hand,

to the census-based data of the National Institute for Statistics and Economic Studies. The 10 individual items that constitute the EDI are: 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 are applied to the smallest French geographical area (Ilôts Regroupés pour l'Information Statistique [IRIS]), the EDI constitutes an ecological index of social deprivation. It allows comparisons between European countries where it has been validated.[14,15] Two studies from our team demonstrated that the EDI was associated with the outcomes of renal transplantation and with the proportion of living-donor transplantation.[16,17]

To our knowledge, there are no data about the effects of social disparities in health, estimated by a European transnational indicator, and preemptive transplantation. Moreover, although 3 studies have evaluated the role of social disparities on access to transplantation using mediation analyses,[18-20] none have examined the mediators that could explain the association between social deprivation and preemptive renal transplantation.

The objective of our study was to assess the association between social deprivation, estimated by the most deprived quintile of the EDI, and preemptive renal transplantation. The objective was also to estimate the direct and indirect effects of social deprivation on the outcome.[21-23]

MATERIALS AND METHODS

Study Population and Data Sources

This was a retrospective study, using the CRISTAL database of the French Biomedicine Agency (Agence de la Biomédecine, Saint-Denis, France) where the data of transplanted patients of 32 French transplantation centers were registered. The patients older than 18 y receiving a first deceased- or living-donor kidney ransplantation between January 1, 2010, and December 31, 2014, and for whom a precise home address in France was provided at registration for the waiting list (required for EDI calculation) were included in the study. Patients who had already been transplanted (renal, cardiac, or liver transplant) or who had received a multiorgan transplantation were excluded. Of the 9205 transplanted patients from the original dataset, home address was missing for 504 of them. There was no statistical difference regarding the patients' characteristics between individuals excluded because of missing address and the other patients. Ultimately, 8701 patients were included.

Study Variables

Event of Interest

The event of interest was preemptive renal transplantation, with either a deceased- or living-kidney donor, among the study population. Preemptive kidney transplantation (PKT) was defined as transplantation with no previous history of dialysis.

Social Deprivation

The explanatory variable was the EDI. The EDI is a validated European ecological index, for which there is a French version,[14] calculated for the smallest geographical scale available in France (IRIS) corresponding to about 2000 inhabitants. Each patient's home address corresponds to an IRIS for which the EDI has been measured and has been interpreted as a proxy of the individual social deprivation. The induced ecological bias of this proxy is considered to be limited because

the accuracy of socioeconomic measures decreases with the size of the geographical unit used.

The EDI was categorized into 5 quintiles to describe the general population (quintile 5 being the most deprived), as recommended by Pornet et al[14] after studying its distribution. Subsequently, as was necessary for the mediation analyses, the EDI was dichotomized and used as a binary variable (quintile 5 versus other quintiles).

Of note, ethnicity could not be studied in our work since the collection of this variable is not authorized by the French law.

Patient Characteristics

Patient information provided at registration for the renal transplant waiting list is collected in the CRISTAL database of the Agence de la Biomédecine. The following variables were extracted: age, sex, body mass index (BMI), underlying nephropathy, diabetes, cardiovascular disease (coronaropathy, myocardial infarction, chronic heart failure, angiopathy, and stroke), tobacco use, hypertension, hepatitis C virus (HCV) serology, cytomegalovirus (CMV) serology, Epstein-Barr virus serology, positive HLA antibodies, blood group, preemptive registration, and preemptive transplantation.

Potential Confounders and Mediators

Our assumptions for potential confounders and mediators were defined based on the literature data (**SDC**, http://links.lww.com/TXD/A357) and their hypothetical relations with quintile 5 of the EDI and PKT are graphically represented in a directed acyclic graph (DAG) (Figure 1).[24]

This study was conducted in the French regulation context regarding living donor transplantation. Patients awaiting renal transplantation, whatever the modality, must be registered on the waiting list for deceased-donor transplantation. That means that even patients due for living donor are registered on the waiting list pending the end of the transplantation work up of their living donor. Consequently, of the patients who have a living donor, there are individuals that accept a proposal for a deceased-donor transplant before the completion of the living-donor transplantation. "Registration with a living donor," which is on the pathway to preemptive transplantation, could have been considered as a marker of the access to LDKT, unfortunately this information is not collected in the registry. We hypothesized that the most deprived patients had a lower likelihood of preemptive transplantation that could be partly explained by a lower access to living donor. As the variable "registration with a living donor" was not available in the database, "LDKT" was used as a proxy and considered as a mediator of the effect of social deprivation on the rate of preemptive transplantation.

Statistical Analyses

For the univariate analysis, characteristics of the complete cohort were described according to the 5 quintiles of the EDI. Categorical data were described by frequencies and percentages.

Using a logistic regression model, 2 bivariate analyses were performed to estimate the association of each covariate with quintile 5 of the EDI and with PKT. Regression splines were used to explore the functional form of the continuous variables "age" and "BMI." As there was no linear relationship between these covariates and the logit event of interest, they were transformed into categorical variables.
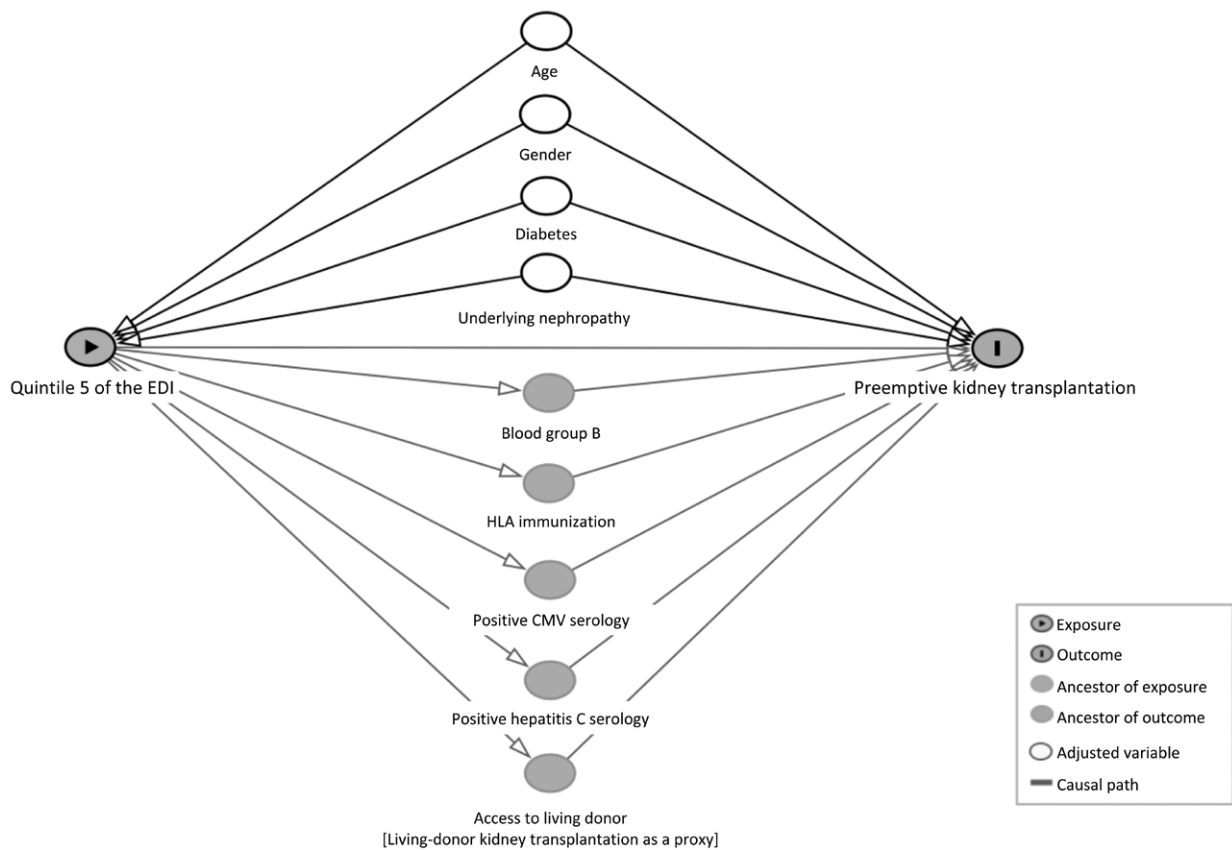
FIGURE 1. Directed acyclic graph describing the causal assumptions in the relationship between social deprivation, estimated by quintile 5 of the European Deprivation Index, and preemptive kidney transplantation (potential confounders and potential mediators). CMV, cytomegalovirus; EDI, European Deprivation Index.

Mediation analyses explore the underlying mechanism by which one exposure variable influences an outcome variable through a mediator variable. The relationship between the exposure variable, the outcome variable, potential confounders, and potential mediators are graphically represented by rows in a DAG (Figure 1). In traditional regression modeling, when controlling for the mediator, the association between the exposure and outcome is reduced.

Based on the DAG, mediation analyses using a counterfactual approach were performed to assess the extent to which the effect of social deprivation on PKT was direct or mediated by other variables.[21-23] Confidence intervals (CIs) of the estimates were obtained using a nonparametric bootstrap procedure.

As there were 5 potential mediators, a mediation analysis with 1 mediator at a time was first performed. Subsequently, a sequential mediation analysis was conducted (*model 1*: single mediator "living-donor transplantation," *model 2*: model 1 + "positive CMV serology," *model 3*: model 2 + "HLA immunization," *model 4*: model 3 + "positive HCV serology," *model 5*: model 4 + "blood group B"). Mediators were entered based on the strength of their association with the outcome in the bivariate analysis.

All mediation analyses were adjusted for age, gender, diabetes, and underlying nephropathy. The "total effect" of the exposure on the outcome was decomposed into a "natural direct effect" (the effect of the exposure on the outcome) and into a "natural indirect effect" (the effect of the exposure on the outcome through a mediator). There were no exposure–mediator or mediator–mediator interactions.

This study using data from the CRISTAL database was conducted with the approval of the French National Ethics Committee (Commission Nationale de l'Informatique et des Libertés).

Statistical analyses were performed using R3.3.3 (R Foundation for Statistical Computing, Vienna, Austria), using medflex and dagitty packages.

RESULTS

Patient Characteristics

Among the 8701 transplant recipients, 2818 patients (32.4 %) were in quintile 5 of the EDI and 1397 (16%) received a PKT. Compared with the patients of the other quintiles, subjects of quintile 5 were younger (older than 60 y: 32% versus 41% in quintile 1, 36% in quintile 2, and 39% in quintiles 3 and 4), were more frequently female (39% in quintile 5 versus 34% in quintiles 1 and 2, 35% in quintile 3, and 36% in quintile 4), and had a higher BMI. Patients in quintile 5 were more frequently diabetic, positive for HCV serology and blood group B (15% in quintile 5 versus 11% in quintiles 1 to 3 and 10% in quintile 4). The rate of HLA immunization was greater in the quintile 5 group than in the other groups (29% in quintile 5 versus 25% in quintiles 1 and 2 and 26% in quintiles 3 and 4). The proportion of PKT decreased from quintile 1 to quintile 5 (20% in quintile 1, 19% in quintile 2, and 17% in quintiles 3 and 4 versus 12% in quintile 5) as did the proportion of living-donor transplants (16% in quintiles 1 and 2, 14% in quintile 3, and 15% in quintile 4 versus 12% in quintile 5). Patient characteristics are presented in Table 1 and **Table S1** (**SDC**, http://links.lww.com/TXD/A357).

Patient characteristics (complete cohort) according to deprivation quintiles of the European Deprivation Index (quintile 5 is the most deprived)

	All (N=8701)	Quintile 1 (N=1272)	Quintile 2 (N=1391)	Quintile 3 (N=1524)	Quintile 4 (N=1696)	Quintile 5 (N=2818)
Patient characteristics						
Age (y)						
18–30	685 (8%)	88 (7%)	98 (7%)	110 (7%)	143 (8%)	246 (9%)
30–60	4839 (56%)	659 (52%)	788 (57%)	821 (54%)	899 (53%)	1672 (59%)
>60	3177 (37%)	525 (41%)	505 (36%)	593 (39%)	654 (39%)	900 (32%)
Gender (female)	3150 (36%)	434 (34%)	470 (34%)	534 (35%)	608 (36%)	1104 (39%)
BMI (kg/m²)						
<20	247 (3%)	36 (3%)	35 (3%)	46 (3%)	49 (3%)	81 (3%)
20–25	4203 (48%)	638 (50%)	675 (49%)	719 (47%)	854 (50%)	1317 (47%)
>25	4251 (49%)	598 (47%)	681 (49%)	759 (50%)	793 (47%)	1420 (50%)
Underlying nephropathy						
Diabetic	895 (10%)	100 (8%)	120 (9%)	138 (9%)	169 (10%)	368 (13%)
Glomerulonephritis	1979 (23%)	309 (24%)	352 (25%)	368 (24%)	401 (24%)	549 (19%)
Interstitial nephritis	789 (9%)	102 (8%)	128 (9%)	144 (9%)	152 (9%)	263 (9%)
PKD (ref)	1650 (19%)	289 (23%)	324 (23%)	320 (21%)	334 (20%)	383 (14%)
Systemic disease	302 (3%)	43 (3%)	48 (3%)	60 (4%)	59 (3%)	92 (3%)
Uropathy	204 (2%)	29 (2%)	37 (3%)	36 (2%)	47 (3%)	55 (2%)
Vascular	866 (10%)	133 (10%)	116 (8%)	132 (9%)	149 (9%)	336 (12%)
Miscellaneous	477 (5%)	73 (6%)	64 (5%)	80 (5%)	87 (5%)	173 (6%)
Unknown	1539 (18%)	194 (15%)	202 (15%)	146 (16%)	298 (18%)	599 (21%)
Diabetes	1466 (17%)	190 (15%)	228 (16%)	228 (15%)	266 (16%)	554 (20%)
Cardiovascular disease	2041 (23%)	301 (24%)	328 (24%)	368 (24%)	379 (22%)	665 (24%)
Tobacco (smoker)	4497 (52%)	611 (48%)	672 (48%)	727 (48%)	843 (50%)	1351 (48%)
Hypertension	5948 (68%)	882 (69%)	952 (68%)	1036 (68%)	1131 (67%)	1947 (69%)
Positive hepatitis C serology	222 (3%)	26 (2%)	35 (3%)	18 (1%)	41 (2%)	102 (4%)
Positive CMV serology	5147 (59%)	602 (47%)	702 (50%)	818 (54%)	983 (58%)	2042 (72%)
Positive EBV serology	8329 (96%)	1213 (95%)	1325 (95%)	1452 (95%)	1626 (96%)	2713 (96%)
HLA antibody class I and/or II > 0%	2309 (27%)	317 (25%)	347 (25%)	395 (26%)	438 (26%)	812 (29%)
Blood group						
B	1043 (12%)	134 (11%)	149 (11%)	172 (11%)	162 (10%)	426 (15%)
Others	7658 (88%)	1138 (89%)	1242 (89%)	1352 (89%)	1534 (90%)	2392 (85%)
Transplantation characteristics						
Preemptive registration	3026 (35%)	532 (42%)	547 (39%)	573 (38%)	584 (34%)	790 (28%)
Preemptive transplantation	1397 (16%)	252 (20%)	268 (19%)	264 (17%)	283 (17%)	330 (12%)
Donor source						
Living donor	1225 (14%)	209 (16%)	220 (16%)	219 (14%)	251 (15%)	326 (12%)
Of which PKT	478 (39%)	94 (45%)	96 (44%)	89 (41%)	92 (37%)	107 (33%)
Deceased donor	7476 (86%)	1063 (84%)	1171 (84%)	1305 (86%)	1445 (85%)	2492 (88%)
Of which PKT	919 (12%)	158 (15%)	172 (15%)	175 (13%)	191 (13%)	223 (9%)

BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PKD, polycystic kidney disease; PKT, preemptive kidney transplantation.

Bivariate Analyses

Patient characteristics of age older than 60 y, female gender, diabetes, positive HCV serology, positive CMV serology, HLA immunization, blood group B, and the underlying nephropathy were associated with quintile 5 of the EDI (Table 2). Patients in quintile 5 were less likely to be transplanted from a living donor and before dialysis initiation (odds ratio [OR]: 0.73 [95% CI: 0.63-0.83], OR: 0.60 [95% CI: 0.52-0.68]).

Factors associated with preemptive transplantation were age older than 30 y, female gender, diabetes, cardiovascular disease, tobacco use, positive HCV serology, positive CMV serology, HLA immunization, blood group B, and underlying nephropathy (Table 3). Quintile 5 of the EDI and living-donor transplantation were associated with preemptive transplantation (OR: 0.60 [95% CI: 0.52-0.68]; OR: 4.57 [95% CI: 3.99-5.22]).

Tables S2 and S3 (SDC. http://links.lww.com/TXD/A357), respectively, represent the comparison of factors between each quintile of the EDI and factors associated with preemptive registration.

Mediation Analyses

After adjustment for potential confounders, the mediation analysis showed a significant total effect (OR: 0.64 [95% CI: 0.55-0.73]) and direct effect of quintile 5 of the EDI on preemptive transplantation. In the mediation analyses performed separately for each mediator, quintile 5 had a significant indirect effect on preemptive transplantation through

TABLE 2.

Bivariate analysis (logistic regression)

Patient characteristics (N = 2818)	OR [95% CI]
Age (y)	
18–30	Ref
30–60	0.94 [0.80-1.11]
>60	0.71 [0.59-0.84]
Gender (female)	1.21 [1.10-1.33]
BMI (kg/m^2)	
<20	1.07 [0.81-1.40]
20–25	Ref
>25	1.10 [1.00-1.20]
Underlying nephropathy	
Diabetic	2.31 [1.94-2.75]
Glomerulonephritis	1.27 [1.09-1.48]
Interstitial nephritis	1.65 [1.37-1.99]
PKD	Ref
Systemic disease	1.45 [1.10-1.89]
Uropathy	1.22 [0.87-1.69]
Vascular	2.10 [1.75-2.51]
Miscellaneous	1.88 [1.51-2.34]
Unknown	2.11 [1.81-2.46]
Diabetes	1.33 [1.19-1.50]
Cardiovascular disease	1.01 [0.91-1.12]
Tobacco (smoker)	0.98 [0.89-1.07]
Hypertension	1.05 [0.95-1.16]
Positive hepatitis C serology	1.80 [1.38-2.36]
Positive CMV serology	2.35 [2.14-2.60]
HLA antibody class I and/or II > 0%	1.19 [1.07-1.31]
Blood group	
B	1.52 [1.33-1.73]
Others	Ref
Donor source (living donor)	0.73 [0.63-0.83]
Preemptive kidney transplantation	0.60 [0.52-0.68]

Factors associated with quintile 5 of the European Deprivation Index.
BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio; PKD, polycystic kidney disease.

TABLE 3.

Bivariate analysis (logistic regression)

Patient characteristics (N = 1397)	OR [95% CI]
Age (y)	
18–30	Ref
30–60	0.71 [0.59-0.87]
>60	0.67 [0.55-0.83]
Gender (female)	1.13 [1.01-1.27]
BMI (kg/m^2)	
<20	1.03 [0.73-1.44]
20–25	Ref
>25	0.93 [0.83-1.04]
Underlying nephropathy	
Diabetic	0.40 [0.31-0.51]
Glomerulonephritis	0.69 [0.58-0.81]
Interstitial nephritis	0.95 [0.77-1.17]
PKD	Ref
Systemic disease	0.30 [0.19-0.46]
Uropathy	1.27 [0.90-1.76]
Vascular	0.46 [0.36-0.58]
Miscellaneous	0.68 [0.51-0.88]
Unknown	0.51 [0.42-0.62]
Diabetes	0.56 [0.46-0.66]
Cardiovascular disease	0.52 [0.44-0.61]
Tobacco (smoker)	0.79 [0.71-0.89]
Hypertension	0.89 [0.79-1.00]
Positive hepatitis C serology	0.43 [0.25-0.68]
Positive CMV serology	0.75 [0.67-0.84]
HLA antibody class I and/or II > 0%	0.76 [0.66-0.87]
Blood group	
B	0.75 [0.61-0.90]
Others	Ref
Donor source (living donor)	4.57 [3.99-5.22]
EDI (quintile 5)	0.60 [0.52-0.68]

Factors associated with preemptive kidney transplantation.
BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio; PKD, polycystic kidney disease.

living-kidney donor (OR: 0.92 [95% CI: 0.89-0.95]). To a lesser extent, positive CMV serology (OR: 0.98 [95% CI: 0.95-1.00], $P < 0.05$), positive HCV serology (OR: 0.99 [95% CI: 0.99-1.00], $P < 0.05$), and blood group B (OR: 0.99 [95% CI: 0.98-1.00], $P < 0.05$) were also mediators of the effect of social deprivation on PKT. Quintile 5 of the EDI had no indirect effect on preemptive transplantation through the HLA immunization (OR: 1.00 [95% CI: 0.99-1.00]). The results of the mediation analysis examining one mediator at a time are displayed in Table 4. When the mediators were entered sequentially in the mediation analyses, the indirect effect of quintile 5 of the EDI through the mediators remained within the same range (OR: 0.92 [95% CI: 0.89-0.95] for model 1, OR: 0.90 [95% CI: 0.87-0.94] for model 2, OR: 0.90 [95% CI: 0.87-0.94] for model 3, OR: 0.90 [95% CI: 0.86-0.93] for model 4, and OR: 0.89 [95% CI: 0.85-0.92] for model 5). The results of the sequential mediation analysis are provided in Table 5.

Additional Analyses

Additional mediation analyses focusing on preemptive registration as the outcome are presented in **Tables S4 and S5** (**SDC**, http://links.lww.com/TXD/A357).

The results of the multivariable analysis stratified by donor type are presented in **Table S6** (**SDC**, http://links.lww.com/TXD/A357). In this analysis, quintile 5 of the EDI was associated with preemptive registration and preemptive transplantation in the deceased-donor kidney transplanted group but not in the living-donor kidney transplanted group. This could be explained by the fact that patients belonging to quintile 5 who received a living-donor transplant may have particular characteristics not measured in our study or may have a different treatment modality. However, the interaction term between EDI (exposure) and donor type (mediator) had no effect on PKT (outcome), which allowed us to conduct the mediation analysis reflecting the natural effect models.

DISCUSSION

Our study showed that in France, social deprivation estimated by the EDI was highly prevalent among transplanted patients and that it was associated with a lower proportion of preemptive renal transplantation directly but also indirectly through living-donor transplantation, which appeared to be the main mediator. Our findings were consistent with the results of previous studies, which highlighted social disparities

Mediation analyses: effects of social deprivation on preemptive kidney transplantation (one mediator at a time)

	Living-donor transplantation		Positive CMV serology		HLA immunization		Positive hepatitis C serology		Blood group B	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Natural direct effect	0.69	[0.61-0.78]**	0.65	[0.57-0.75]**	0.64	[0.56-0.73]**	0.64	[0.55-0.73]**	0.64	[0.56-0.73]**
Natural indirect effect	0.92	[0.89-0.95]**	0.98	[0.95-1.00]*	1.00	[0.99-1.00]	0.99	[0.99-1.00]*	0.99	[0.98-1.00]*
Total effect	0.64	[0.56-0.73]**	0.63	[0.56-0.73]**	0.63	[0.55-0.73]**	0.63	[0.55-0.73]**	0.63	[0.55-0.73]**

The analyses were adjusted for confounders: age, sex, diabetes, and underlying nephropathy.
*$P < 0.05$.
**$P < 0.001$.
CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio.

in access to preemptive transplantation[9-12] and confirmed that the EDI can be used in the nephrology field of social deprivation.[12,16-18,25,26] The factors that may explain this association could depend on the healthcare system, the recipient, and the donor, as well as the physician.

Disparities in access to primary care, necessary for referral to a nephrologist, may partially explain the lower proportion of preemptive transplantation in the most deprived patients compared with the other transplanted patients. It has been shown that individuals with a greater income received more prescription medication and more often visited medical specialists and underwent advanced imaging procedures.[27] In one study from the United States, routine healthcare visits were a mediator between socioeconomic status and chronic kidney disease (CKD).[28] In France, inequities in access to primary care have been recently described in the general population.[29]

A faster decline in renal function in the most deprived population could also affect the timing of the nephrology referral. It has been demonstrated that low socioeconomic status was associated with a higher risk of chronic diseases[30] and with risk factors for CKD progression.[28] Lower socioeconomic status was associated with albuminuria, estimated glomerular filtration rate decline, and end-stage renal disease in previous reports.[31,32] In Europe, low education levels were associated with CKD progression.[33] In a report from the United Kingdom, socially deprived populations had a higher risk of severe CKD at presentation to a renal service.[34] Moreover, a French study showed that the most deprived patients had a higher risk of requiring emergency dialysis than the other patients,[26] whereas the emergency start was associated with a lower chance of being waitlisted in a recent study.[35] Lower socioeconomic and educational status resulted in delayed

nephrology referral,[36] even though late referral is known to reduced transplantation access.[37]

An association among health literacy, socioeconomic status, and CKD has been demonstrated.[38] Thus, the lack of understanding of what CKD is and what it involves is influenced by socioeconomic status and could also affect access to healthcare and referral to nephrology.

Moreover, there is a potential association between social deprivation and geographic isolation, which would suggest that distance to the transplantation center might delay registration on the waiting list; however, previous studies among dialysis patients have reported controversial results.[39,40] To the best of our knowledge, there are no data about the effect of the distance from patient home to transplantation center and preemptive registration. Socioeconomic status could impact the whole process of kidney transplantation from the potential recipient to the potential donor because of difficulty in navigating the health system. Navigator programs may help the most deprived subjects move through the complex pathway that leads to transplantation.[41]

The cost associated with the transplantation workup may as well decrease access to preemptive registration on the waiting list. Disparities between private centers or for-profit ownership of dialysis facilities were described regarding access to the exams required for registration.[42] In a recent US study, disparities in patients' access to PKT were associated with the type of health insurance.[11] However, in Sweden, despite a universal healthcare coverage, low income was also associated with lower registration on the waiting list for renal transplantation.[43]

The sequential mediation analysis we conducted has identified LDKT as being the main and above all modifiable

Sequential mediation analyses: effects of social deprivation on preemptive kidney transplantation

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Natural direct effect	0.69	[0.61-0.78]	0.70	[0.62-0.80]	0.70	[0.62-0.80]	0.71	[0.62-0.81]	0.72	[0.63-0.82]
Natural indirect effect	0.92	[0.89-0.95]	0.90	[0.87-0.94]	0.90	[0.87-0.94]	0.90	[0.86-0.93]	0.89	[0.85-0.92]
Total effect	0.64	[0.56-0.73]	0.64	[0.56-0.73]	0.64	[0.55-0.73]	0.64	[0.55-0.73]	0.64	[0.55-0.73]

The analyses were adjusted for confounders: age, sex, diabetes, and underlying nephropathy.
Model 1: mediation analysis with a single mediator—living-donor transplantation.
Model 2: mediation analysis with 2 mediators—living-donor transplantation and positive CMV serology.
Model 3: mediation analysis with 3 mediators—living-donor transplantation, positive CMV serology, and HLA immunization.
Model 4: mediation analysis with 4 mediators—living-donor transplantation, positive CMV serology, HLA immunization, and positive hepatitis C serology.
Model 5: complete mediation analysis with the 5 mediators described in the DAG—living-donor transplantation, positive CMV serology, HLA immunization, positive hepatitis C serology, and blood group B.
CI, confidence interval; CMV, cytomegalovirus; DAG, directed acyclic graph; OR, odds ratio.

mediator between social deprivation and PKT. To our knowledge, our study is the first to focus on the mediators involved in the causal pathway between social deprivation and PKT. Indeed, in a pediatric French cohort, Driollet et al[18] studied the mediators between the EDI and graft failure. In the United Kingdom, Bailey et al[19] studied the indirect effect of education and income on LDKT. And last, in a US study by Murphy et al,[20] socioeconomic status was a mediator between ethnicity and access to registration and renal transplantation.

To our knowledge, there is no mediation analysis that has evaluated LDKT as an outcome. Large-scale studies conducted in Australia, the United Kingdom, and the United States showed that socially deprived patients had lower access to LDKT.[9-11] Since socially deprived relatives are exposed to the same risk factors as deprived recipients,[28] the prevalence of chronic diseases among potential donors could reduce the possibility of organ donation in the most disadvantaged populations. Data about living donors in the United States showed that living donors were more frequently employed than the general population.[44] Gill et al[13] reported that the rate of LDKT was greater in the highest income population and that the least deprived living donors had greater access to medical specialists who performed the transplantation workup. It can also be speculated that difference in health literacy related to socioeconomic status, cultural, and religious factors may influence the willingness toward living organ donation.[45-47] To decrease ethnic disparities in access to living-donor transplantation, web programs for education on LDKT have been developed.[48]

Finally, the socioeconomic status of patients may influence physicians' perception and practice. In support of this, a qualitative study conducted in Australia and New Zealand highlighted that nephrologists tended to consider that the most socially disadvantaged patients were less likely to receive a living-donor kidney.[49]

In our mediation analyses, positive CMV serology, known to be associated with an increased risk of cardiovascular disease[50]; hepatitis C, which is more prevalent in disadvantaged populations[51]; and blood group B had an indirect effect on preemptive transplantation, but the magnitude of the effect was marginal compared with living-donor.

Our study has limitations. Residual confounders not collected in the database may affect the association between the EDI and preemptive transplantation. As an example, ethnicity has not been studied because the collection of this data is not authorized in France. The EDI potentially contains mediators of the relationship between social deprivation and PKT, such as foreign nationality, no access to a car, low level of education, unemployment, single-parent family, or household ≥6 people.[14] Last, the association between the EDI and preemptive transplantation was estimated among transplanted patients, whereas a study of patients registered for renal transplantation would have provided a more accurate estimation.

Our work demonstrated that social deprivation estimated by the EDI was associated with PKT. Our study emphasized that the effect of social deprivation on preemptive transplantation was mainly mediated by living-donor transplantation. This result is interesting since, unlike the other mediators highlighted in our study, living-donor transplantation is a modifiable factor. Further studies are needed to explore the role of social deprivation on LDKT. To increase preemptive renal transplantation in the most deprived populations, measures should be implemented to promote living-donor

transplantation, targeting both practitioners and patients. Physicians should be able to promote health literacy and to provide information about living-donor transplantation tailored to the patients' health literacy.[52] Widespread use of web or mobile programs for shared decision aid in the treatment of CKD should be encouraged[48,53] to help inform socially deprived patients.

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