ORIGINAL ARTICLE

Is there sex disparity in vascular access at dialysis initiation in France? A mediation analysis using data from the Renal Epidemiology and Information Network registry

Mathilde Beaumier1,2, Maxence Ficheux1, Cécile Couchoud3, Mathilde Lassalle3, Ludivine Launay2, Cécile Courivaud3,4, Aurélien Tiple3,5, Thierry Lobbedez1,2 and Valérie Chatelet1,2; on behalf of the REIN registry

1Centre Universitaire des Maladies Rénales, CHU de Caen Avenue Côte de Nacre, Caen, France, 2U1086 Inserm, “ANTICIPE,” Centre de Lutte Contre le Cancer François Baclesse, Caen, France, 3REIN Registry, Biomedecine Agency, Saint-Denis-La-Plaine, France, 4Service de Néphrologie, Dialyse et Transplantation Rénale, CHU de Besançon, Besançon, France and 5Service de Néphrologie, Dialyse et Transplantation, CHU de Clermont-Ferrand, Clermont-Ferrand, France

Correspondence to: Thierry Lobbedez; E-mail: lobbedez-t@chu-caen.fr

ABSTRACT

Background. This study was conducted to estimate the direct effect of sex on the proportion of hemodialysis (HD) catheters used at dialysis initiation and to investigate whether predialysis care or socioeconomic status acted as a mediator of the sex effect.

Methods. Patients who started dialysis between January 1, 2017, and June 30, 2018, in France were included using the data of the Renal Epidemiology and Information Network (REIN) registry. We performed logistic regression to study the association between sex and the proportion of HD catheters used. A mediation analysis with a counterfactual approach was carried out to evaluate whether there was an indirect effect of sex through the proxies of predialysis care (hemoglobin, albumin levels, glomerular filtration rate [GFR] at dialysis initiation) and socioeconomic status. Because an interaction between sex and social deprivation has been identified, we performed a subgroup analysis on deprived and nondeprived patients.

Results. The study included 16,032 patients, and the sex ratio (male to female) was 10,405:5,627. In the multivariable analysis, women were associated with a greater risk of starting dialysis with a catheter (odds ratio [OR], 1.32 [95% confidence interval (CI): 1.23–1.42]). There was an indirect effect of sex on the proportion of HD catheters through proxies for predialysis care [hemoglobin < 11 g/dL [OR, 1.03 (95% CI: 1.02–1.04)], glomerular filtration rate < 7 mL/min [OR, 1.05 (95% CI: 1.04–1.07)]] and socioeconomic status. Because an interaction between sex and social deprivation has been identified, we performed a subgroup analysis on deprived and nondeprived patients.

Conclusions. Women were associated with a higher risk of starting dialysis through an HD catheter. The effect of sex was mediated by predialysis care, particularly for deprived patients.
**LAY SUMMARY**

Arteriovenous fistula is the preferred vascular access for patients treated by hemodialysis. American studies showed that women were more strongly associated with catheter use at dialysis initiation compared with men, not explained by anatomical differences. This study was conducted to estimate the effect of sex on catheter use at dialysis initiation and to investigate whether predialysis care or socioeconomic status acted as an intermediate. We included 16,032 patients who started dialysis between January 1, 2017, and June 30, 2018, in France. Women were associated with a greater risk of starting dialysis with a catheter. There was an indirect effect through proxies for predialysis care. We found that for deprived patients, there was no direct effect of sex on catheter use, which could lead to the hypothesis that predialysis care explains the role of sex in catheter use. Conversely, because the direct effect of sex remained significant for less deprived patients, one could argue that other mediators could explain the relationship, such as patients choice.

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**GRAPHICAL ABSTRACT**

Women are less likely to start hemodialysis with a fistula than men. We investigated whether predialysis care or socioeconomic status acted as a mediator of the sex effect on CVC proportion.

**Methods**

- Retrospective multicenter observational study

16,032 patients
Starting dialysis between 1 Jan 2017 and 30 June 2018

- Direct effect of sex on CVC use
- Indirect effect through proxies of predialysis care

| Direct effect | Indirect effect |
|---------------|----------------|
| Alb < 30 g/L  | 1.08 (1.04–1.12) |
| Hb < 11 g/dL  | 1.02 (1.00–1.04) |
| eGFR < 7 ml/min | 1.03 (1.01–1.04) |

**Results**

- 50.9% CVC at dialysis start
- Multivariable analysis: ↑ CVC for female OR 1.32 (1.23–1.42)

| Deprived patients | Less deprived patients |
|-------------------|------------------------|
| Alb < 30 g/L      | 1.08 (1.05–1.10)       |
| Hb < 11 g/dL      | 1.03 (1.02–1.04)       |
| eGFR < 7 ml/min   | 1.05 (1.04–1.07)       |

**Conclusion:** Females are associated with a higher risk of starting dialysis with a CVC. The effect of sex is mediated by predialysis care, particularly for deprived patients.

**Keywords:** dialysis vascular access, European Deprivation Index, mediation analysis, sex disparities, social deprivation

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**INTRODUCTION**

In 2010, more than 2 million people received dialysis worldwide, a number will exceed 5 million by 2030 [1]. The annual cost of dialysis varies by country from US$13,000 to US$47,000 per patient per year [2]. In France, 49,271 patients were treated by dialysis in 2018 [3], with a cost of more than €3 billion per year according to the French national health care system. It is widely accepted that disparities exist between men and women with chronic kidney disease [4, 5]. Data from the US Renal Data System and the Renal Epidemiology and Information Network (REIN) registry showed that men represent 70% of the patients treated with kidney replacement therapy [3, 6], and women have less access to kidney transplantation than men [7]. It has recently been suggested that sex may influence the choice of the dialysis modality, with women more prone to being treated by peritoneal dialysis (PD) than men [8]. Sex influences the outcomes of dialysis, with women experiencing a poorer quality of life, more hospitalizations, and a higher risk of mortality at younger than 45 years of age compared with men [4]. We recently demonstrated that sex affects the outcome of PD as women have a lower risk of transfer to hemodialysis (HD) and a lower risk of peritonitis than men [9].
Arteriovenous fistula (AVF) is the preferred vascular access for patients treated by HD [10]. It has been shown that women are less likely to start HD with a fistula than men [11, 12]. In addition, being a woman is a risk factor both for having a central venous catheter (CVC) at initiation of kidney replacement and for chronic HD [13]. A recent study demonstrated that after starting HD, women spent a longer with a CVC and were less frequently transitioned to an AVF [14].

The causes of the larger proportion of CVC use at dialysis initiation in women remain unknown because there have been conflicting data regarding significant anatomical differences between men and women that could lead to vascular access failure [15, 16]. Access to the health care system, predialysis care, social deprivation, or psychosocial factors could explain these findings. CVC use is associated with minority ethnicity and with social deprivation [17]. In France, women are more deprived than men [18]. Women also start dialysis with a lower glomerular filtration rate (GFR) and lower hemoglobin and serum albumin levels, which could reflect differences in predialysis care [12, 19, 20]. We hypothesized that the effect of sex on CVC use at the start of dialysis was partly explained by differences between women and men in predialysis care and socioeconomic status.

This study was conducted to estimate the direct effect of sex on the proportion of CVC use at initiation of kidney replacement and to investigate whether predialysis care or socioeconomic status acted as a mediator of the sex effect.

MATERIALS AND METHODS

Study population and data sources

This retrospective study used data from the REIN registry [21]. Patients older than 18 years who started dialysis in France between January 1, 2017, and June 30, 2018, were included in the study. Patients from the French overseas territories and patients without follow-up in the REIN registry or with a duration of follow-up shorter than 2146 hours of diagnosis or an emergency start, defined as a first dialysis initiated without a central venous catheter (CVC), were excluded. Patient and treatment characteristics included age, sex, underlying nephropathy, hemoglobin, predialysis erythropoiesis-stimulating agent (ESA) use, occupational status, and the number of nephrology consultations before dialysis in the year preceding initiation of dialysis. Nutritional status was assessed by body mass index (BMI) and serum albumin. Comorbidities included diabetes, cardiovascular disease (CVD) (defined as stroke, transient ischemic attack, dysrhythmia, peripheral vascular disease, coronary heart disease, or abdominal aortic aneurysm), congestive heart failure (CHF), smoking status, chronic respiratory disease, active cancer, and liver disease (defined as cirrhosis, hepatitis C virus infection, or hepatitis B virus infection). Circumstances of dialysis initiation were collected: first dialysis with a CVC, estimated GFR (eGFR) at dialysis initiation using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and emergency start, defined as a first dialysis initiated because of a life-threatening issue requiring dialysis within 24 hours of diagnosis.

Social deprivation evaluated by the European Deprivation Index

Because of a lack of individual socioeconomic markers in the REIN registry, we used the European Deprivation Index (EDI) as a proxy of the individual level of deprivation. The EDI is an ecological index based on fundamental needs. Data from the European Union Statistics on Income and Living Conditions, which considered the specificity of the sociocultural environment, and from the French census were used. The EDI was determined from individual perceptions of deprivation, also called ‘subjective poverty,’ and from objective poverty. It was then calculated as the sum of 10 weighted variables: low level of education, defined as less than the first stage of secondary-level education; unemployment; nonhomeowner status; foreign nationality; household with six or more people; single-parent household; unskilled farm worker; no access to car; no exclusive use of a bathtub or shower; and overcrowded housing, defined by more than one person per room [22].

The score from the French EDI is a continuous score and was calculated in 2011 for each neighborhood, called an ‘IRIS’ (Îlot Regroupé pour l’Information Statistique), to reduce ecological bias. In France, the IRIS is the smallest geographical unit. It corresponds to 2000 inhabitants and is defined by the Institut National de la Statistique et des Etudes Economiques). The EDI was divided into quintiles in the general population (quintile 5 was the most deprived). Based on mailing address, we assigned each patient an IRIS and thus an EDI.

Exposure, potential confounders, and mediators

The hypothetical relations among the exposure, confounders, mediators, and outcome were graphically represented by a direct acyclic graph [23, 24]. Assumptions for potential confounders and mediators were defined based on the literature data (Supplementary Data 1). The exposure was the sex (female or male). The mediators were social deprivation, serum albumin level, and hemoglobin level in the month before starting dialysis and eGFR collected at the start of dialysis, which were dichotomized and considered proxies for predialysis care (serum albumin < 30 g/L, hemoglobin level < 11 g/dL, eGFR < 7 mL/min) [20, 25]. Because of the rate of missing data, we did not use the number of nephrology consultations before dialysis in the analysis. As recommended in mediation analysis, we tested the interactions between the exposure and the mediator. There was a significant interaction between sex and social deprivation, indicating that the association between sex and CVC use was different between deprived individuals and other participants. Consequently, we modified the direct acyclic graph post hoc, removed social deprivation from the mediators, stratified and performed the analysis in the most deprived patient subgroup and in the other patient subgroup.

Statistical analysis

Continuous variables were described by the median values and the first and third quartiles. Categorical variables were described by frequencies and percentages. Continuous variables were separated into categories if there was no linear relationship between the predictor and the outcome with regression splines. Patients were classified in the quintiles of the French general population. The EDI was dichotomized (quintile 5 vs
other quintiles) and used as a binary variable. The eGFR was dichotomized with a threshold of 7 mL/min according to the criteria used in the IDEAL study to define late dialysis initiation [26]. We used a logistic regression model for the statistical analysis. Multivariable analysis was performed with the confounders; subsequently, the mediators were added to the model.

A mediation analysis was performed to explore the relationship between sex and the proportion of CVC use at dialysis start by decomposing the total effect into direct and indirect effects through mediators. In a counterfactual approach for the mediation analysis [27], we created two data sets with fictive exposure and a fictive mediator for each patient based on the observed data. The occurrence of the outcome was estimated by using a weighting-based approach, and the outcome was that which would have been observed if the participants had been exposed to the fictive exposure or mediator. A nonparametric bootstrap procedure was used to calculate the confidence intervals of the odds ratios. Mediation analysis was performed by entering one mediator at a time and adjusting for confounding factors (age, underlying nephropathy, BMI, CHF, CVD, active cancer, chronic respiratory disease, and liver disease). The analysis was performed in the most deprived subgroup and in the other patient subgroup. Furthermore, to provide more information, the HD analysis was performed separately after the exclusion of PD patients.

### Sensitivity analysis

According to the VanderWeele method, sensitivity analysis was performed by calculating a bounding factor called the ‘e-value’ [28, 29]. The e-value is defined as the minimum odds ratio that reflects the effect of the unmeasured confounders on the exposure and on the outcome to cancel the observed association. The higher the e-value, the more robust the results.

### Missing data

Multiple imputation by chained equation was performed for all missing data. Twenty imputed data sets were created, and regression coefficients were obtained according to Rubin’s rules [30]. Patient characteristics on the imputed data set are displayed in Supplementary Data 2.

Statistical analysis was performed using R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using the ‘mice’ and ‘medflex’ packages.

The REIN registry has the support of the French National Ethics Committee (Commission Nationale de l’Informatique et des Libertés). The study was conducted within the frame of this authorization.

### RESULTS

#### Patient characteristics

Among the 16,032 patients in our study, the median age was 71.4 years. There were 10,405 male (64.9%) and 5,627 female (35.1%) patients; 1,683 patients were treated by PD (10.5%), and 14,349 patients (89.5%) were treated by HD (89.5%); 4,774 (29.8%) patients belonged to the most deprived quintile of the EDI. In total, 4,177 patients (26.1%) started dialysis in an emergency context, 8,168 patients (50.9%) started dialysis with a CVC, and 6,481 patients (40.4%) were treated with an ESA.

Female patients had fewer comorbidities than male patients: CVD (40.7% vs 57%; P < .001), CHF (22.9% vs 28.5%; P < .001), chronic respiratory disease (9.6% vs 15.8%; P < .001), active malignancy (8.3% vs 13.1%; P < .001), and liver disease (3.2% vs 4.3%; P < .001). The proportion of diabetes was similar between the two groups (P = .75). Female patients more often experienced obesity (26.6% vs 20%; P < .001) and malnutrition (20.7% vs 17.5%; P < .001). There was a larger proportion of CVC use at dialysis start in female patients than in male patients (53% vs 49.8%; P < .001). The proportion of emergency starts was similar between the two groups.

Of the 8,168 patients who started dialysis with a CVC, 5,185 were male (63.5%) and 2,983 were female (36.5%). Among these patients, 2,449 (30%) belonged to the fifth quintile of the EDI. The median age was 71.8 years. The median number of consultations in the year before dialysis start was two, and 2,716 patients (33.3%) were treated with an ESA. There was an important proportion of patients with comorbidities among those who started with a CVC: diabetes (47.6%), CVD (54.5%), CHF (31.8%), chronic respiratory disease (14%), liver disease (4.9%), and malnutrition (26.4%). Patients characteristics are displayed in Table 1.

#### Multivariable analysis

**Most deprived patients subgroup**

After adjusting for confounders, female patients had higher odds of starting dialysis with a CVC (odds ratio [OR], 1.17 [95% confidence interval (CI): 1.02–1.33]). There was no significant association when the mediators were included in the multivariable analysis (OR, 1.06 [95% CI: 0.92–1.21]). In both models (with and without mediators), dialysis initiation with a CVC was associated with age, CVD, CHF, active cancer, and liver disease. Starting dialysis with a CVC was associated with albuminemia less than 30 g/L [OR, 3.68 [95% CI: 2.98–4.55]], hemoglobin level less than 11 g/dL [OR, 1.44 [95% CI: 1.23–1.68]], and an eGFR below 7 ml/min at dialysis initiation [OR, 1.48 [95% CI: 1.29–1.70]]. Obese patients and those with polycystic kidney disease had a lower risk of starting dialysis with a CVC.

**Other patients subgroup**

After adjustment for confounders and mediators, female patients were more likely to start dialysis with a CVC [OR, 1.33 [95% CI: 1.20–1.47]]. CVC use at dialysis initiation was also associated with age, BMI, CVD, CHF, active cancer, chronic respiratory disease, liver disease, albuminemia less than 30 g/L, hemoglobin level below 11 g/dL, and GFR under 7 ml/min.

The results of the multivariable analysis are displayed in Tables 2 and 3.

#### Mediation analysis

In the mediation analysis performed in the most deprived patient subgroup, there was no direct effect of sex on the odds of CVC use, whereas sex had an indirect effect mediated by albuminemia under 30 g/L [female-to-male OR, 1.08 [95% CI: 1.04–1.12]], hemoglobin level under 11 g/dL [OR, 1.02 [95% CI: 1.00–1.04]], and eGFR below 7 ml/min [OR, 1.03 [95% CI: 1.01–1.04]]. In the other patient subgroup, sex had a significant direct effect on CVC use at dialysis initiation when each mediator (albuminemia, hemoglobin level, eGFR) was entered one at a time into the analysis [OR, 1.37 [95% CI: 1.24–1.51], 1.43 [95% CI: 1.30–1.58], 1.40 [95% CI: 1.27–1.55], respectively]. The association was partially mediated by albuminemia less than 30 g/L [OR, 1.08 [95% CI: 1.05–1.10]], hemoglobin level under 11 g/dL [OR, 1.03...
Table 1. Patient characteristics by sex

|                         | n = 16 032 | Male n = 10 405 | Female n = 5627 | P-value |
|-------------------------|------------|----------------|-----------------|---------|
| EDI, n(%)               |            |                |                 | <.001   |
| Quintile 1              | 1861 (11.6)| 1302 (12.5)    | 559 (9.9)       |         |
| Quintile 2              | 2157 (13.5)| 1442 (13.9)    | 715 (12.7)      |         |
| Quintile 3              | 2390 (14.9)| 1603 (15.4)    | 787 (14.0)      |         |
| Quintile 4              | 3009 (18.8)| 1977 (19.0)    | 1032 (18.3)     |         |
| Quintile 5              | 4774 (29.8)| 2902 (27.9)    | 1872 (33.3)     |         |
| Missing                 | 1841 (11.5)| 1179 (11.3)    | 662 (11.8)      |         |
| Dialysis modality, n(%)|            |                |                 | .028    |
| PD                      | 1683 (10.5)| 1051 (10.1)    | 632 (11.2)      |         |
| HD                      | 14 349 (89.5)| 9354 (89.9)| 4950 (88.8)    |         |
| Age (years), median (IQR)| 71.4 (61.3–80.4)| 71.5 (61.3–80.4)| 71 (59.8–80.8)| .003    |
| Underlying nephropathy, n(%)|    |                |                 | <.001   |
| Glomerulonephritis      | 1634 (10.2)| 1129 (10.9)    | 505 (9.0)       |         |
| Vascular/hypertensive nephropathy | 4291 (26.8)| 2997 (28.8)   | 1294 (23.0)     |         |
| Diabetic nephropathy    | 3612 (22.5)| 2307 (22.2)    | 1305 (23.2)     |         |
| Polycystic kidneys      | 884 (5.5)  | 467 (4.5)      | 417 (7.4)       |         |
| Pyelonephritis          | 696 (4.3)  | 452 (4.3)      | 244 (4.3)       |         |
| Other or unknown        | 4915 (30.7)| 3053 (29.3)    | 1862 (33.1)     |         |
| Comorbidities, n(%)     |            |                |                 |         |
| Diabetes                | 7440 (46.4)| 4839 (46.5)    | 2601 (46.2)     | .751    |
| Missing                 | 115 (0.7)  | 74 (0.7)       | 41 (0.7)        |         |
| CVD*                    | 8217 (51.3)| 5928 (57.0)    | 2289 (40.7)     | <.001   |
| Missing                 | 533 (3.3)  | 327 (3.1)      | 206 (3.7)       |         |
| CHF                     | 4251 (26.5)| 2964 (28.5)    | 1287 (22.9)     | <.001   |
| Missing                 | 368 (2.3)  | 241 (2.3)      | 127 (2.3)       |         |
| Smoking                 |            |                |                 | <.001   |
| Nonsmoker               | 7494 (46.7)| 3888 (37.4)    | 3606 (41.4)     |         |
| Former smoker           | 4241 (26.5)| 2357 (23.5)    | 1884 (33.9)     |         |
| Smoker                  | 1737 (10.8)| 1308 (12.6)    | 429 (7.6)       |         |
| Missing                 | 2560 (16.0)| 1552 (14.9)    | 1008 (17.9)     |         |
| Chronic respiratory disease | 2186 (13.6)| 1645 (15.8)  | 541 (9.6)       | <.001   |
| Missing                 | 381 (2.4)  | 243 (2.3)      | 138 (2.5)       |         |
| Cancer                  | 1830 (11.4)| 1364 (13.1)    | 466 (8.3)       | <.001   |
| Missing                 | 329 (2.1)  | 217 (2.1)      | 112 (2.0)       |         |
| Liver disease           | 625 (3.9)  | 447 (4.3)      | 178 (3.2)       | <.001   |
| Missing                 | 653 (4.1)  | 422 (4.1)      | 231 (4.1)       |         |
| Nutritional status, n(%)|            |                |                 | <.001   |
| BMI ≥30 kg/m²           | 3579 (22.3)| 2081 (20.0)    | 1498 (26.6)     | <.001   |
| Missing                 | 2158 (13.5)| 1352 (13.0)    | 806 (14.3)      |         |
| Albuminemia <30 g/L     | 2989 (18.6)| 1822 (17.5)    | 1167 (20.7)     | <.001   |
| Missing                 | 4447 (27.7)| 2893 (27.8)    | 1554 (27.6)     |         |
| Number of nephrology consults | 0.323  |              |                |         |
| Median (IQR)            | 4 (2–6)    | 4 (2–6)        | 4 (2–6)         |         |
| Missing                 | 6509 (40.6)| 4246 (40.8)    | 2263 (40.2)     |         |
| Predialysis anemia care, n(%)|   |                |                 |         |
| Hemoglobin <11 g/dL     | 10 337 (64.5)| 6557 (63.0) | 3780 (67.2)     | <.001   |
| Missing                 | 1688 (10.5)| 1120 (10.8)    | 568 (10.1)      |         |
| Predialysis ESA treatment| 6481 (40.4)| 3957 (38.0)    | 2524 (44.9)     | <.001   |
| Missing                 | 2147 (13.4)| 1404 (13.5)    | 743 (13.2)      |         |
| Emergency start, n(%)   | 4177 (26.3)| 2717 (26.1)    | 1460 (25.9)     | .875    |
| Missing                 | 663 (4.3)  | 425 (4.1)      | 238 (4.1)       |         |
| First dialysis with CVC, n(%)| 8168 (50.9)| 5185 (49.8)  | 2983 (53.0)     | <.001   |
| Missing                 | 1284 (8.0) | 798 (7.7)      | 486 (8.6)       |         |
| eGFR (CKD-EPI) at dialysis initiation (mL/min), n(%)|   |                |                 | <.001   |
| GFR <7                  | 5260 (32.8)| 3082 (29.6)    | 2178 (38.7)     |         |
| Missing                 | 1488 (9.3) | 982 (9.4)      | 506 (9.0)       |         |
| Occupational status, n(%)|            |                |                 | <.001   |
| Active                  | 1398 (8.7) | 980 (9.4)      | 418 (7.4)       |         |
| Inactive                | 1793 (11.2)| 929 (8.9)      | 864 (15.4)      |         |
| Unemployed              | 188 (1.2)  | 127 (1.2)      | 61 (1.1)        |         |
| Retired                 | 9641 (60.1)| 6535 (62.8)    | 3106 (55.2)     |         |
| Missing                 | 3012 (18.8)| 1834 (17.6)    | 1178 (20.9)     |         |

*Includes stroke or transient ischemic attack, dysrhythmia, peripheral vascular disease, coronary heart disease or abdominal aortic aneurysm. IQR: interquartile range.
Is there sex disparity in vascular access at dialysis initiation in France?

Table 2. Multivariable analysis among deprived patients: factors associated with CVC use at dialysis start

|                        | Model without mediators |                     | P-value | Model with mediators |                     | P-value |
|------------------------|-------------------------|---------------------|---------|----------------------|---------------------|---------|
| **OR (95% CI)**        |                         |                     |         |                      |                     |         |
| Sex                    |                         |                     |         |                      |                     |         |
| Male [Reference]       | 1.17 (1.02–1.33)        | .027               |         | 1.06 (0.92–1.21)     | .437               |         |
| Female                 |                         |                     |         |                      |                     |         |
| Age (years)            |                         |                     |         |                      |                     |         |
| ≤50                    | 1.45 (1.20–1.75)        | <.001              |         | 1.37 (1.12–1.67)     | .002               |         |
| 50–80                  | [Reference]             |                     |         | [Reference]          |                     |         |
| >80                    | 1.15 (0.98–1.35)        | .096               |         | 1.27 (1.07–1.51)     | .007               |         |
| BMI (kg/m²)            |                         |                     |         |                      |                     |         |
| ≤30                    | 0.79 (0.67–0.92)        | .004               |         | 0.85 (0.71–0.99)     | .050               |         |
| >30                    |                         |                     |         |                      |                     |         |
| Underlying nephropathy |                         |                     |         |                      |                     |         |
| Glomerulonephritis     | [Reference]             |                     |         | [Reference]          |                     |         |
| Hypertensive nephropathy| 1.03 (0.81–1.31)       | .790               |         | 1.17 (0.91–1.50)     | .236               |         |
| Diabetic nephropathy   | 1.02 (0.81–1.30)        | .858               |         | 1.07 (0.83–1.37)     | .622               |         |
| Polycystic kidneys     | 0.28 (0.19–0.41)        | <.001              |         | 0.38 (0.26–0.56)     | <.001              |         |
| Pyelonephritis         | 1.18 (0.83–1.68)        | .368               |         | 1.32 (0.91–1.92)     | .150               |         |
| Other or unknown       | 1.45 (1.15–1.83)        | .002               |         | 1.53 (1.19–1.97)     | <.001              |         |
| CVD                    | 1.17 (1.01–1.34)        | .034               |         | 1.15 (0.99–1.34)     | .077               |         |
| CHF                    | 1.91 (1.63–2.23)        | <.001              |         | 2.09 (1.77–2.48)     | <.001              |         |
| Active cancer          | 1.44 (1.16–1.80)        | .001               |         | 1.28 (1.01–1.62)     | .040               |         |
| Chronic respiratory disease | 1.11 (0.92–1.34)    | .264               |         | 1.12 (0.92–1.36)     | .265               |         |
| Liver disease          | 1.96 (1.42–2.71)        | <.001              |         | 1.68 (1.19–2.36)     | .003               |         |
| Albuminemia (g/L)      |                         |                     |         |                      |                     |         |
| ≥30                    |                         |                     |         |                      | 3.68 (2.98–4.55)   | <.001   |
| <30                    |                         |                     |         |                      |                     |         |
| Hemoglobin (g/dL)      |                         |                     |         |                      | [Reference]        | [Reference] |
| ≥11                    |                         |                     |         |                      | [Reference]        | [Reference] |
| <11                    |                         |                     |         |                      | 1.44 (1.23–1.68)   | <.001   |
| eGFR (mL/min)          |                         |                     |         |                      |                     |         |
| ≥7                     |                         |                     |         |                      | [Reference]        | [Reference] |
| <7                     |                         |                     |         |                      | 1.48 (1.29–1.70)   | <.001   |

[95% CI: 1.02–1.04], and eGFR below 7 mL/min [OR, 1.05 [95% CI: 1.04–1.07]]. The results are displayed in Table 4.

Patients treated by HD

The multivariable analysis showed similar results to the analysis performed on the whole population. In the most deprived patient subgroup, sex had a direct effect on CVC use, and sex had an indirect effect mediated by serum albumin levels below 30 g/dL [OR, 1.08 [95% CI: 1.03–1.12]] and an eGFR under 7 mL/min [OR, 1.03 [95% CI: 1.01–1.05]] but no indirect effect through hemoglobin level. In the other patient subgroup, sex had a direct effect on CVC use [OR, 1.40 [95% CI: 1.27–1.55], 1.48 [95% CI: 1.34–1.64], 1.44 [95% CI: 1.31–1.60]]. There was an indirect effect through serum albumin level less than 30 g/dL [OR, 1.08 [95% CI: 1.05–1.11]], hemoglobin level below 11 g/dL [OR, 1.03 [95% CI: 1.01–1.04]], and an eGFR below 7 mL/min [OR, 1.05 [95% CI: 1.04–1.07]]. The results are displayed in Supplementary Data 3 and 4. The results of the mediation analysis are provided in Supplementary Data 5.

Discussion

Our study confirms the results of previous studies showing that sex is associated with the type of vascular access at dialysis initiation [11, 12]. Our work underlines the fact that the role of sex in CVC use is partially explained by differences in proxies of predialysis care. Interestingly, our study showed that, in the most deprived subgroup, sex had no direct effect on CVC use, which could lead to the hypothesis that, in this particular subgroup, predialysis care explains the role of sex in catheter use. Conversely, because the direct effect of sex remained significant in the other patient subgroup, one could argue that other mediators could explain the relationship in participants who did not belong to the most deprived group.

Sex-based inequity in vascular access creation for dialysis is a matter of concern because it is well established that, compared with a fistula, being treated with a CVC is associated with a higher risk of infection [31], hospitalization [32], central venous stenosis [33], mortality [32, 34] and extra costs [31]. In two different studies, women had a higher risk of starting HD with a CVC than men [11, 12]. In patient on dialysis, women were also associated with CVC use [13]. It was demonstrated that female patients spent longer on a CVC, and fewer were transitioned to AVF than male patients [14]. In contrast, there was no association between sex and the type of vascular access in other studies [35, 36].

There have been conflicting data regarding the role of anatomic differences between men and women on the type of vascular access for HD. The smaller vessel size of women compared with men could jeopardize vascular access creation, leading to a larger proportion of CVC use at the start of dialysis. Small
Table 3. Multivariable analysis among less deprived patients: factors associated with CVC use at dialysis start

| Mediator                              | Model without mediators | Model with mediators |
|---------------------------------------|-------------------------|----------------------|
|                                       | OR (95% CI)             | P-value              |
|                                       | OR (95% CI)             | P-value              |
| Sex                                   |                         |                      |
| Male                                  | [Reference]             | [Reference]          |
| Female                                | 1.47 (1.33–1.62)        | <.001                |
|                                       | 1.33 (1.20–1.47)        | <.001                |
| Age (years)                           |                         |                      |
| ≤50                                   | 1.47 (1.25–1.73)        | <.001                |
|                                       | 1.55 (1.30–1.83)        | <.001                |
| 50–80                                 | [Reference]             | [Reference]          |
| >80                                   | 1.13 (1.02–1.25)        | .024                 |
|                                       | 1.20 (1.08–1.34)        | .001                 |
| BMI (kg/m²)                           |                         |                      |
| ≤30                                   | [Reference]             | [Reference]          |
| >30                                   | 0.70 (0.63–0.78)        | <.001                |
|                                       | 0.75 (0.67–0.85)        | <.001                |
| Underlying nephropathy                |                         |                      |
| Glomerulonephritis                    | [Reference]             | [Reference]          |
|                                       | [Reference]             | [Reference]          |
| Hypertensive nephropathy              | 0.99 (0.85–1.17)        | .920                 |
|                                       | 1.14 (0.96–1.35)        | .128                 |
| Diabetic nephropathy                  | 1.06 (0.90–1.26)        | .468                 |
|                                       | 1.13 (0.95–1.35)        | .163                 |
| Polycystic kidneys                    | 0.41 (0.32–0.52)        | <.001                |
|                                       | 0.54 (0.43–0.69)        | <.001                |
| Pyelonephritis                        | 1.30 (1.02–1.65)        | .017                 |
|                                       | 1.38 (1.07–1.77)        | .013                 |
| Other or unknown                      | 1.69 (1.45–1.97)        | <.001                |
|                                       | 1.82 (1.55–2.13)        | <.001                |
| CVD                                   | 1.27 (1.14–1.41)        | <.001                |
|                                       | 1.31 (1.17–1.46)        | <.001                |
| CHF                                   | 1.62 (1.46–1.80)        | <.001                |
|                                       | 1.68 (1.51–1.88)        | <.001                |
| Active cancer                         | 1.60 (1.39–1.84)        | <.001                |
|                                       | 1.45 (1.26–1.68)        | <.001                |
| Chronic respiratory disease           | 1.21 (1.06–1.38)        | .005                 |
|                                       | 1.25 (1.09–1.43)        | .002                 |
| Liver disease                         | 1.67 (1.31–2.14)        | <.001                |
|                                       | 1.52 (1.18–1.97)        | .001                 |
| Albuminemia (g/L)                     |                         |                      |
| ≥30                                   | [Reference]             | [Reference]          |
| <30                                   | 2.81 (2.45–3.21)        | <.001                |
| Hemoglobin (g/dL)                     |                         |                      |
| ≥11                                   | [Reference]             | [Reference]          |
| <11                                   | 1.48 (1.34–1.64)        | <.001                |
| eGFR (mL/min)                         |                         |                      |
| ≥7                                    | [Reference]             | [Reference]          |
| <7                                    | 1.52 (1.37–1.69)        | <.001                |

Table 4. Mediation analysis

| Mediators                              | Albininemia <3 g/L, OR (95% CI) | Hemoglobin <11 g/dL, OR (95% CI) | eGFR <7 mL/min, OR (95% CI) |
|----------------------------------------|---------------------------------|---------------------------------|-----------------------------|
|                                       | Direct effect                    | Indirect effect                 | E value                     |
| Deprived patients                      | 1.08 (0.95–1.23)                | 1.02 (1.00–1.04)                | 1.03 (1.01–1.04)            |
|                                       | 1.37                            | 1.16                            | 1.21                        |
| Less deprived patients                 | 1.37 (1.24–1.51)                | 1.43 (1.30–1.58)                | 1.40 (1.27–1.55)            |
|                                       | 2.08                            | 2.21                            | 2.15                        |
|                                       | 1.08 (1.05–1.10)                | 1.03 (1.02–1.04)                | 1.05 (1.04–1.07)            |
|                                       | 1.37                            | 1.21                            | 1.28                        |

The analyses were adjusted for age, underlying nephropathy, CVD, CHF, active cancer, BMI, and liver disease.

*P* < .05

Vessel size could also explain the larger proportion of arteriovenous grafts among women [12, 13]. In two studies, however, there was no difference between men and women regarding the venous diameters of the upper extremities [15, 16]. Interestingly, in these two studies, there was a significant difference between women and men in arterial diameter, but the vessel diameter was larger than 2 mm, which is the minimal diameter recommended for AVF [37]. In another study [38], there was no association between sex and the likelihood of undergoing vascular access surgery before starting dialysis. Conversely, some studies have demonstrated that failure to create vascular access for HD was more frequent in women than in men. One study showed that the fistula success rate was higher in men than in women; in this report, fistula in women resulted in greater risks of failure.
Is there sex disparity in vascular access at dialysis initiation in France?

FIGURE 1: Directed acyclic graph describing the causal assumptions between sex and catheter use at dialysis initiation

to mature and a higher risk of early thrombosis [16]. In a Swiss study, the risk of early AVF failure, defined by vascular access thrombosis or no maturation 6 months after fistula creation, was higher in women than in men [39].

The fact that our study showed that predialysis care partially explained CVC use in women, especially in the most deprived patients, is a matter of concern because it is a modifiable factor. Our results suggest that female patients experience less effective predialysis care than male patients because they experience malnutrition and anemia at dialysis start. Late nephrology referral is negatively associated with fistula at the start of dialysis [11, 40]. Surprisingly, several studies have shown that female patients had a greater likelihood than male patients of predialysis follow-up [12, 38]. In addition, male sex was associated with a higher number of unplanned dialysis starts in the United Kingdom [41]. In a recent study from France, female patients were not associated with an emergency start [42]. Access to primary care is compulsory for access to nephrology clinics. In a study from the United States, female patients had more office visits than male patients irrespective of ethnicity, age, education, health care insurance, and work status [43]. Female patients had a greater likelihood of starting dialysis with an eGFR less than 5 mL/min in the United States and in Canada, even after adjustment for insurance status and employment [19, 44].

Previous studies in nephrology have shown that female patients are more deprived than males [18, 45]. Ethnic minority patients, who are associated with social deprivation, initiated HD less frequently with a fistula than White patients in the United States [17]. These disparities remained significant even after considering insurance status and duration of nephrology care.
Similarly, patients with no insurance had a fourfold increase in the odds of CVC use at dialysis start compared with patients on Medicaid. Patients identified some barriers to AVF creation: limited social and financial resources, lack of transportation, and lack of information [46]. Women can experience difficulties in organizing medical appointments that could explain CVC use because AVF creation requires many consultations and a short hospitalization. Women had a higher prevalence of accommodation and availability barriers than men, leading to unmet needs or delayed care [47].

Patients choice regarding vascular access creation may also explain our findings. Limited health literacy was associated with choice of catheter [48], but it was more frequent among men and could not explain the greater odds of CVC placement among women [49]. The Dialysis Outcomes and Practice Patterns Study data showed that when patients were asked to indicate their preferences for vascular access, 58% of women preferred a fistula vs 69% of men. The two main reasons for the choice were the willingness to avoid ‘large needles’ and ‘bleeding after dialysis’ [50]. Finally, aesthetic considerations could limit women’s choices. It would be interesting to further explore this issue in qualitative studies.

Our study had limitations. The number of predialysis nephrology consultations was not used because of the missing data rate in addition to eGFR at nephrologist referral, so late referrals are not registered in the REIN database. Moreover, data about failed fistula creation before dialysis initiation were not available in the registry. Information about individual socioeconomic status, such as income or education level, is not collected in the registry. The area-level socioeconomic index is by nature associated with ecological bias. Unmeasured confounders may also affect and bias the results. The E values were less than 1.40, meaning that an unobserved confounder with an OR of 1.4 on the exposure and the outcome could fully explain the results. Although this matter is debatable, sex was used as a proxy of gender that would have been more adequate as it refers to socially constructed roles and behaviors.

CONCLUSION

Our study shows that in France, female patients are more likely to start dialysis with a CVC. Thanks to a mediation analysis, we emphasize that the effect of sex on CVC use is mediated by proxies of predialysis care. Other mediators could explain the association between sex and CVC use in patients who do not belong to the most deprived group. Therefore, further studies—notably, qualitative studies—are necessary to explore other pathways that lead to CVC use at initiation of dialysis.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly for ethical reasons.

CONFLICT OF INTEREST STATEMENT

None declared. This paper has not been published previously in whole or part, except in abstract format.

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