Effect of Community Characteristics on Familial Clustering of End-Stage Renal Disease

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Key Words

End-stage renal disease • Environment/neighborhood • Familial aggregation • Geocode • Socioeconomic status

Abstract

Background: Lower socioeconomic status is generally associated with an increased risk of end-stage renal disease (ESRD). The relationship between community characteristics reflecting socioeconomic status and familial aggregation of common forms of ESRD has not been studied. **Methods:** Demographic data and family history of ESRD were collected from 23,880 incident dialysis patients in ESRD Network 6 between 1995 and 2003. Addresses were geocoded and linked to the 2000 census 5-digit zip code-level database that includes community demographic, social and economic characteristics. Clustering of patients having a family history of ESRD at the community level was accounted for using a generalized estimating equations (GEE) model. Multivariate analysis estimated associations between family history of ESRD and community-level characteristics. **Results:** Twenty-three percent of patients reported a family history of ESRD. After adjusting for individual demographic characteristics, multivariate analyses failed to reveal statistically significant relationships between a family history of ESRD and indica-

tors of community socioeconomic status such as median household income, percentage high school graduates, percentage vacant housing units or ethnic composition. **Conclusions:** Although select community measures of lower socioeconomic status may contribute to the familial clustering of ESRD, non-socioeconomic factors, potentially inherited, appear to be more important contributors to familial aggregation of the common forms of ESRD.

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Introduction

Lack of access to adequate medical care and lower socioeconomic status (SES) are associated with an increased risk of developing chronic kidney disease (CKD) [1]. Familial aggregation of kidney failure has long been recognized in common complex forms of kidney disease, including end-stage renal disease (ESRD) attributed to chronic glomerular disease, diabetes mellitus and hypertension-associated nephropathy [2–4]. The role of environmental exposures, SES, and inherited factors in causation of ESRD remains unclear in these complex kidney disorders. It is important to address this question, as prevention of CKD can be optimized by un-

Fig. 1. Network 6 family history of ESRD study (n = 59,167).

derstanding the relative roles that environmental effects (e.g., lack of access to physicians and appropriate medications) and inheritance play in nephropathy susceptibility [5].

Genetic factors clearly influence the development of kidney disease as exemplified by the association of the *MYH9* gene with focal segmental glomerulosclerosis, human immunodeficiency virus-associated nephropathy, and the disease labeled ‘hypertension-associated ESRD’ in African-Americans [6–8]. It is estimated that 70% of all non-diabetic cases of ESRD in African-Americans are directly attributable to variation in this gene. In contrast, the present analyses were performed to assess the role of environmental factors involving neighborhood characteristics that reflect SES in the common familial forms of ESRD.

Methods

Sample and Data

Individual-level data were derived from ESRD Network 6 Family History (FH) of ESRD Study participants [3, 4]. The overall dataset included 59,167 incident dialysis patients starting dialysis therapies between January 1, 1995 and December 31, 2003. The standardized data collection instrument included questions on FH of ESRD in 1st-, 2nd-, and 3rd-degree relatives, age, sex, self-reported ethnicity, number of 1st-degree relatives, etiology of CKD from the CMS 2728 Medical Evidence Report form (containing the designated cause of ESRD as reported by treating physicians), employment status and patient address. This voluntary questionnaire was presented to all dialysis providers to be completed by patients initiating renal replacement therapy in ESRD Network 6 dialysis facilities serving the states of North Carolina, South Carolina and Georgia in the southeastern US. To restrict the analysis to common forms of ESRD [typically attributed to chronic glomerular diseases (primary and secondary forms, e.g., lupus nephritis), diabetes mellitus and hypertension-associated nephropathy], we excluded cases with inherited cystic kidney disease, hereditary nephritis, urologic disease, drug-induced nephritis or surgical nephrectomy. ESRD cases with ‘unknown’ etiologies of kidney disease were included, since many have undiagnosed glomerular and interstitial diseases. The study protocol was approved by the Institutional Review Board at Wake Forest University School of Medicine in Winston-Salem, N.C., USA.

Community-level data were obtained from the 2000 US Census Summary Files 1 and 3 using American Factfinder at <http://factfinder.census.gov> [9]. Five-digit zip code-level census data for demographic composition, SES and residential mobility were extracted. The 2000 US Census and the Network 6 data were linked by geocoded address (5-digit zip code).

After exclusion criteria were applied, the final sample size was 23,880 (fig. 1). FH data were not provided by 30,429 patients, most often due to refusal of their dialysis providers (large dialysis organizations) to permit facility staff to administer the voluntary questionnaire to patients. As previously reported, participation rates fell during the later years of the study; however, rates of a positive FH of ESRD did not change over time, suggesting that there was no inherent selection bias among study participants [4]. Incident dialysis patients lacking valid geocoded addresses (n = 2,543) or residing in non-Network 6 states (n = 11) were also excluded. Eight hundred and eighty additional patients were excluded because their primary cause of renal failure was: missing; an inherited cystic renal disease; hereditary nephritis; congenital renal failure; neoplasm/tumor, or traumatic/surgical removal of kidneys. Patients less than 18 years of age (n = 118) were excluded, as were those with self-reported ethnicity other than African-American or European-American (n = 849), and those without recent (prior 6 month) employment status (n = 445). Finally, 12 patients were excluded due to lack of census data at the level of 5-digit zip code, leaving a total of 23,880 eligible patients.

Measures

Dependent Variable

The primary outcome ‘FH of ESRD’ was considered present if a patient reported having a 1st-, 2nd- or 3rd-degree relative with ESRD.

Table 1. Community-level variables and definitions: 2000 US census 5-digit zip code-level data

Variable	Census definition
<i>Socioeconomic indicators</i>	
Median household income	Income in 1999, USD
Poverty ¹	Poverty status in 1999 – below poverty level, %
Educational attainment	High school graduates (includes equivalency) or college degree, %
<i>Residential mobility</i>	
Employment status ¹	Unemployed civilian population 16 years and over, %
Housing tenure	Vacant housing units, %
<i>Ethnic composition</i>	
European-American ¹	Caucasian, %
African-American	Black or African-American, %
Hispanic ¹	Hispanic or Latino (of any ethnicity), %

¹ Not included in the final model building process due to multi-collinearity.

Independent Variables

Individual-Level Variables. Individual demographic characteristics, employment status and primary cause of ESRD were obtained from ESRD Network 6. These characteristics included age at ESRD onset, gender, ethnicity, number of 1st-degree relatives, prior 6 month fulltime employment status (before dialysis initiation), and diabetes as primary cause of renal failure.

Individual Geocoded Address. Full street addresses were available from subjects. Geocoded patient addresses were derived from Network 6 data using ArcGIS 9.2 [10]. The appropriate census 5-digit zip code was identified for each patient's geocoded address and mapped to census 5-digit zip code area. The patient's geocoded 5-digit zip code was used to link ESRD Network 6 individual-level data with census 2000 community-level (5-digit zip code) data.

Community-Level Variables. 'Community' is defined as a '5-digit zip code geographic area'. All community-level variables used in the analysis were based on this definition and we use the terms 'community characteristics' and 'census 5-digit zip code-level data' interchangeably. Community-level characteristics include socioeconomic indicators, residential mobility, and ethnic composition. Table 1 lists and defines these community-level variables. We categorized each community-level variable into quartiles based on its distribution in the 1,652 5-digit zip code communities and treated them as ordinal variables in the analyses.

Statistical Analysis

Patients within a community are likely to be more similar to one another compared to patients in other communities, since community populations represent intact social groups [11, 12].

Those reporting a relative with ESRD ('positive FH') were modeled using generalized estimating equations (GEE) for correlated binary responses [13] and for generalized linear models with repeated measures using PROC GENMOD with the REPEATED statement. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for all other variables in the model. Data were analyzed using Statistical Analysis Software (SAS) version 9.1 (2004).

Results

Model Building

Differences in outcome measures were initially modeled among 3 ethnic categories (European-American, African-American, and other). Analyses were limited to European-American and African-American participants since there was limited power to assess differences between 3 ethnic groups due to the small sample of Hispanics, Asians and other ethnic groups.

Several community-level SES variables were significantly correlated with each other. To screen for multicollinearity, all community-level variables were checked using Pearson's correlation coefficients and computing variance inflation factors by regression analysis. After considering the correlation coefficients and variance inflation factors, we excluded community poverty, unemployment, European-American ethnic composition, and Hispanic ethnic composition variables in our final model. The remaining 4 community-level variables were included in the final model: percent African-American ethnic composition, percent high school graduate or higher attained level of education, percent vacant housing units, and median household income (table 1), along with 6 individual-level variables (gender, age at ESRD, ethnicity, number of 1st-degree relatives, 6-month fulltime employment status prior to dialysis and etiology of ESRD).

Description of the Individual and Community Characteristics

Table 2 lists individual-level characteristics of the study sample. The mean (SD) age at ESRD onset of the 23,880 patients was 60.6 (15.2) years, 50.3% were female, 57.2% African-American, 46.5% had diabetes, and 15.9% were employed fulltime prior to ESRD. Their mean (SD) number of 1st-degree family members was 8.0 (5.7), and 23% (5,425) reported a FH of ESRD. The 35,287 non-participating incident ESRD patients in Network 6 appeared comparable to the cases, as 49.9% were female, 54.8% African-American, 41.9% had diabetes, and age at ESRD was 59.7 years.

Table 2. Individual-level characteristics of the 23,880 study subjects

Variables	Mean	SD
Age, years	60.6	15.2
Number of 1st-degree relatives	8.0	5.7
	n	%
Gender		
Female	12,013	50.3
Male	11,867	49.7
Ethnic group		
African-American	13,658	57.2
European-American	10,222	42.8
Fulltime employment		
Yes	3,791	15.9
No	20,089	84.1
Primary cause of ESRD		
Diabetes	11,105	46.5
Other	12,775	53.5
Family history of ESRD		
Yes	5,425	22.7
No	18,455	77.3

Table 3 lists community-level characteristics. In the 1,652 communities, the median African-American composition was 20.9%, median percent below the poverty level 13.4%, median percent with high school or college education 43.5%, median percent vacant housing units 9.8%, and median household income USD 34,765.

Individual and Community Correlates of FH of ESRD

Five of six individual-level indicators (including age at ESRD, gender, ethnicity, number of 1st-degree family members, and etiology of ESRD) had significant associations with the odds of having a FH of ESRD, while none of the community indicators had significant associations (table 4). Specifically, the predicted odds of having a FH of ESRD were decreased by approximately 1% for each 1-year increase in age (for those aged 18 or older). The predicted odds of having a FH of ESRD were increased by 4% for each 1-number increase in number of 1st-degree family members. The predicted odds of a FH of ESRD were approximately 24% higher for female than male patients. African-American patients, compared to European-American, had 2.3 times higher predicted odds of a FH of ESRD. Patients with diabetes as cause of ESRD, compared to non-diabetic ESRD, had a 1.16-times higher predicted odds of a FH of ESRD. Significant relationships

Table 3. Community-level characteristics in 1,652 zip code communities: 2000 US census 5-digit zip code-level data

Variable	Mean (SD)	Median
Socioeconomic indicators		
Median household income, USD	37,085 (12,340)	34,765
Poverty ¹ , %	14.6 (7.7)	13.4
High school or college education, %	43.6 (5.0)	43.5
Residential mobility		
Unemployment ¹ , %	3.5 (2.9)	3.0
Housing tenure (vacant), %	12.2 (9.7)	9.8
Ethnic composition		
African-American, %	26.0 (22.2)	20.9
Hispanic ¹ , %	3.3 (4.6)	1.9
European-American ¹ , %	69.5 (22.5)	73.5

¹ Not included in the final model building process to avoid multi-collinearity.

were not detected between individual SES and FH of ESRD.

After adjustment for 6 individual demographic characteristics, multivariate analyses revealed no statistically significant relationships between FH of ESRD and community-level characteristics reflecting SES (table 4). The PROC GENMOD and PROC GLIMMIX analyses were also run as sensitivity analyses and results were not different (data not shown). We performed multivariate analyses on FH of ESRD limited to participants reporting either 1st- or 2nd-degree relatives with ESRD. Similar results were obtained (data not shown).

Discussion

Familial aggregation of the common causes of ESRD has been appreciated worldwide [14]. It is important to determine whether shared environmental risk factors and lower SES are associated with this clustering, as these factors have been strongly linked to sporadic cases of kidney disease. The present analyses used the ESRD Network 6 'FH of ESRD' database to evaluate demographic and clinical information in 23,880 incident ESRD patients residing in the southeastern United States, and excluded cases with Mendelian disorders (polycystic kidney disease and hereditary nephritis) and environmental causes of kidney failure (obstructive uropathy and surgical nephrectomy). These data were linked with publically available geocode information from the year 2000 census

Table 4. Final multivariate models for family history of ESRD (n = 23,880)

Parameter	OR	95% CI
<i>Individual-level characteristics</i>		
Age	0.99	0.98–0.99*
Gender		
Female	1.24	1.16–1.32*
Male (reference)		
Ethnicity		
African-American	2.32	2.15–2.51*
European-American (reference)		
Number of 1st-degree family members	1.04	1.03–1.04*
Primary Cause of ESRD		
Diabetes	1.16	1.09–1.23*
Other (reference)		
Prior 6-month fulltime employment		
Yes	1.05	0.96–1.15
Part time or no employment (reference)		
<i>Community-level characteristics</i>		
Community racial composition (% African-American)		
Quartile 4 (≥39.8%)	0.94	0.82–1.08
Quartile 3 (20.9–39.7%)	1.00	0.87–1.15
Quartile 2 (7.4–20.8%)	1.02	0.89–1.17
Quartile 1 (<7.4%) (reference)		
High school graduate or college		
Quartile 4 (≥46.5%)	1.04	0.92–1.18
Quartile 3 (43.5–46.4%)	0.99	0.88–1.12
Quartile 2 (40.8–43.4%)	1.04	0.92–1.18
Quartile 1 (<40.8%) (reference)		
Vacant housing units		
Quartile 4 (≥13.8%)	1.07	0.94–1.23
Quartile 3 (9.8–13.7%)	1.12	1.00–1.27
Quartile 2 (6.8–9.7%)	1.03	0.94–1.14
Quartile 1 (<6.8%) (reference)		
Median household income (USD)		
Quartile 4 (≥41,354) (reference)		
Quartile 3 (34,765–41,353)	0.98	0.84–1.13
Quartile 2 (29,207–34,764)	1.05	0.93–1.19
Quartile 1 (<29,207)	1.03	0.92–1.16
OR = Odds ratio; 95% CI = 95% confidence interval.		
* p < 0.0001.		

5-digit zip code-level database. Among these voluntary study participants, 18,455 denied having relatives with ESRD and 5,425 (22.7%) reported a FH of ESRD. After adjustment for family size, we demonstrated that incident dialysis patients having a FH of ESRD did not appear more likely to reside in geocodes reflecting economically disadvantaged regions, relative to those in sporadic cases of ESRD. Individual prior 6-month fulltime employment and community ethnic composition, community median

family income and community level of educational attainment did not differ significantly among geocodes for those with, versus without relatives on dialysis. Given the large size of this database and the relatively high frequency of individuals with relatives on dialysis, the lack of significant differences in these parameters suggests that community-level SES and education attainment are not major contributors to familial causes of ESRD, particularly from diseases such as diabetes, hypertension and glomerulonephritis. Interestingly, Ward [1] reported that associations between measures of SES and kidney disease differed based upon etiology of nephropathy. Individuals with diabetes-associated nephropathy had more profound effects from SES than did those with the Mendelian disorder autosomal dominant polycystic kidney disease, with intermediate effects in those with lupus nephritis [1].

There are several important limitations to this report. Our results relied on data from geocoding, not direct information from participants. However, we have previously reported the accuracy of geocode data [15]. In addition, collecting this volume of information directly from nearly 24,000 incident dialysis patients over a 9-year time-frame would be challenging. It remains possible that some participants incorrectly reported their FH or that their relatives later developed ESRD. We contacted a random sampling of African-American participants to confirm the accuracy of their FH. Direct participant contact revealed that 88% of cases provided the same FH information as was listed in the ESRD Network 6 FH of ESRD database. Another limitation is use of zip code-level census data as proxies for community characteristics. Zip code-level data are often from regions smaller than ‘communities’, especially in highly populated urban areas. In contrast, zip codes often include multiple communities in less densely populated rural areas. Additional research remains to be performed on the influence of community SES and FH of ESRD using data from smaller geographical units, as they become available. The ESRD Network 6 ‘FH of ESRD’ did not collect information on the prevalence of relatives with CKDs that had not yet progressed to ESRD. Renal REGARDS collected this information in a population-based US sample and revealed that African-Americans with a FH of ESRD more often had eGFR of <60 ml/min, relative to African-Americans without a FH [16]. Interestingly, this effect was not observed in European-Americans. The potential impact of a lack of CKD data from relatives in our report is unclear. We suspect that families with two (or more) relatives with ESRD are far more likely to have additional relatives with CKD

based upon the strong heritability of measures of subclinical nephropathy (albuminuria and GFR) in families [17]. Finally, development of ESRD could cause individuals to move to areas characterized by lower SES as a result of an inability to work. There is no a priori reason to suspect that this occurs more often in those with a FH of ESRD, relative to those with sporadic ESRD.

In summary, familial clustering of the common causes of ESRD does not appear to be substantially impacted by measures of lower SES in communities where patients reside. The lack of strong relationships between familial ESRD and lower SES is in direct contrast to the results reported in sporadic cases of ESRD (those without relatives on dialysis). It is likely that inherited factors have a substantial effect on familial clustering of ESRD in kidney disease attributed to diabetes mellitus, high blood pressure and chronic glomerular disorders. These data make a strong case for contacting all close relatives of in-

cident dialysis patients to recommend annual screening for subclinical nephropathy and renal disease risk factors. We may ultimately reduce the burden of ESRD by improving treatment for proteinuria and renal risk factors earlier in members of families at high risk of kidney disease by virtue of having additional affected members.

Acknowledgements

This work was supported in part by NIH grant RO1 DK 070941 (B.I.F.). The data reported here have been supplied by the Southeastern Kidney Council, ESRD Network 6, while under CMS contract HHSM-500-2006-NW006C. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the Southeastern Kidney Council or the Centers for Medicare and Medicaid Services.

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