KI REPORTS
KIReports.org
CLINICAL RESEARCH

Geographic Variation and US County Characteristics Associated With Rapid Kidney Function Decline

Benjamin Bowe[1], Yan Xie[1], Hong Xian[1,2], Min Lian[3] and Ziyad Al-Aly[1,3,4]

[1]Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, Missouri, USA; [2]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri, USA; [3]Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri, USA; and [4]Department of Medicine, Division of Nephrology, VA Saint Louis Health Care System, Saint Louis, Missouri, USA

Introduction: Geographic variation in the prevalence of chronic kidney disease and incidence of end-stage renal disease has been previously reported. However, the geographic epidemiology of rapid estimated glomerular filtration rate (eGFR) decline has not been examined.

Methods: We built a longitudinal cohort of 2,107,570 US veterans to characterize the spatial epidemiology of and examine the associations between US county characteristics and rapid eGFR decline.

Results: There were 169,029 (8.02%) with rapid eGFR decline (defined as eGFR slope < -5 ml/min per 1.73 m^2/year). The prevalence of rapid eGFR decline adjusted for age, race, gender, diabetes, and hypertension varied by county from 4.10%–6.72% in the lowest prevalence quintile to 8.41%–22.04% in the highest prevalence quintile (P for heterogeneity < 0.001). Examination of adjusted prevalence showed substantial geographic variation in those with and without diabetes and those with and without hypertension (P for heterogeneity < 0.001). Cohort participants had higher odds of rapid eGFR decline when living in counties with unfavorable characteristics in domains including health outcomes (odds ratio [OR] = 1.15; confidence interval [CI] = 1.09–1.22), health behaviors (OR = 1.08; CI = 1.03–1.13), clinical care (OR = 1.11; CI = 1.06–1.16), socioeconomic conditions (OR = 1.15; CI = 1.09–1.22), and physical environment (OR = 1.15; CI = 1.01–1.20); living in counties with high percentage of minorities and immigrants was associated with rapid eGFR decline (OR = 1.25; CI = 1.20–1.31). Spatial analyses suggest the presence of cluster of counties with high prevalence of rapid eGFR decline.

Discussion: Our findings show substantial geographic variation in rapid eGFR decline among US veterans; the variation persists in analyses stratified by diabetes and hypertension status; results show associations between US county characteristics in domains capturing health, socioeconomic, environmental, and diversity conditions, and rapid eGFR decline.

Kidney Int Rep (2017) **2,** 5–17; http://dx.doi.org/10.1016/j.ekir.2016.08.016
KEYWORDS: disparity in kidney disease; eGFR decline; geographic information systems; geographic variation; kidney function; spatial epidemiology

Geographic information systems provide an important platform to advance our understanding of the relationship between geography and human health and disease.[1–3] Tanner *et al.*[4] examined the geographic epidemiology of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States and reported substantial geographic variations in the prevalence of CKD and incidence of ESRD, and that CKD prevalence only modestly correlated with ESRD incidence suggesting that the burden of CKD does not explain geographic variation in ESRD incidence. Mills *et al.*[5] showed that the global burden of CKD is high, and that significant variation exists in the prevalence of CKD between high-income countries and low- and middle-income countries. Brück *et al.*[6] examined the geographic variation in CKD prevalence in the European continent and identified substantial variation that followed the same pattern in analyses stratified by status of diabetes mellitus and hypertension—chronic diseases generally considered major drivers of CKD prevalence—suggesting that variation in CKD prevalence is likely to be due to factors other than those traditional drivers. The development of CKD and ESRD

Correspondence: Ziyad Al-Aly, Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, 915 North Grand Boulevard, 151-JC Saint Louis, Missouri 63106, USA. E-mail: zalaly@gmail.com

Received 2 July 2016; revised 20 August 2016; accepted 22 August 2016; published online 30 August 2016

is inherently dependent on the decline in estimated glomerular filtration rate (eGFR), where faster (or more rapid) rate of eGFR decline not only leads to earlier manifestation of kidney disease (whether development of CKD or ESRD), but is also associated with a significant increase in risk of all-cause mortality, cardiovascular mortality, hospitalizations, and readmissions.[7–13]

The rate of eGFR decline varies at the individual patient level, and much is known about individual risk factors associated with rapid kidney function decline.[14,15] The prevalence of rapid eGFR decline might also vary by geography; however, the spatial epidemiology of longitudinal changes in kidney function including rate of eGFR decline and of particular interest rapid eGFR decline has not been characterized. Furthermore, although geographic attributes of pre-ESRD nephrology care have been described, data on the relationship between geographic attributes, social, economic, physical and environmental conditions of communities, and rate of kidney function decline are lacking.[16–19]

The Department of Veterans Affairs operates a national integrated network of health care systems guided by centrally developed policies where eligible veterans have access to the same health care resources nationwide—a factor that may reduce heterogeneity of care practices. We aimed to characterize the spatial epidemiology of rapid eGFR decline among US veterans, identify US county characteristics associated with rapid eGFR decline, and to undertake spatial cluster analyses to identify areas with high prevalence (and low prevalence) of rapid eGFR decline.

MATERIALS AND METHODS

Patients

Using administrative data from the US Department of Veterans Affairs (VA), we identified users of the VA Health Care System who had an outpatient serum creatinine between 1 October 2002 and 30 September 2003 with no prior history of ESRD, dialysis, or kidney transplant, and designated the date of last eGFR measurement in this time frame as time zero (T_0) (n = 2,462,191). Patients were further selected on having at least one other eGFR ≥90 days after T_0 (n = 2,287,495), and followed until 30 September 2013. Participants were then limited to those in the continental United States and Hawaii (n = 2,250,428) who had data on all covariates, yielding an analytic cohort of 2,107,570 (Figure 1). The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

Data Sources

We used Department of Veterans Affairs databases including inpatient and outpatient medical Statistical Analysis System (SAS) datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics, location based on Federal Information Processing Standard county codes, and comorbidity information based on Current Procedural Terminology codes, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes associated with inpatient and outpatient encounters.[20–23] The VA Decision Support System Laboratory Results file (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient serum creatinine measurements.[20,21,24] The VA Vital Status and Beneficiary Identification Records Locator Subsystem files provided demographic characteristics and death follow-up through 30 September 2013.[20,21] United States Renal Data System (USRDS) data from the VA Centers for Medicare and Medicaid Services were used in assessing ESRD status.[25] The

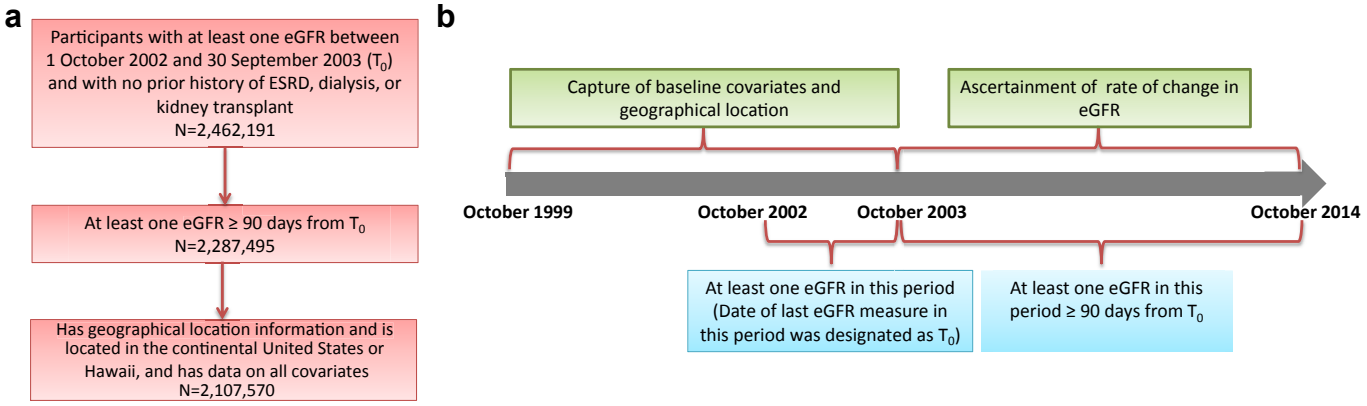

Figure 1. Cohort construction. (a) Flow diagram of cohort assembly. (b) Timeline of cohort selection. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

2000 census was used to define geographical boundaries for maps. County-level variable data were obtained from the 2014 County Health Rankings national datasets.[26,27] The County Health Rankings data are publically available and include a wide scope of county-level information with more than 50 variables from national sources including the Center for Disease Control, Medicare, the US Department of Agriculture, the Behavior Risk Factor Surveillance System, the American Community Survey, and others. Among those, we curated a list of variables that could be compared across state.[26,27] A complete list of variables used in this analysis including data source, definition, and categorization is provided in Supplementary Table S1.[26]

Primary Predictor Variable

The primary predictor variable for all analyses was county. For each patient, we found the recorded Federal Information Processing Standard county code, pertaining to the patients residential county, most proximal and before time zero in the MED SAS inpatient and outpatient data. Counties were matched geometrically to the 2000 Census bureau shapefile. There were data for at least one patient in 3139 counties, with a median (interquartile range) number of patients per county of 238 (103, 562). In additional analyses, we examined the association between ecologic county-level characteristics, including rurality, poverty rate, and the percentage of African Americans, and odds of rapid eGFR decline.

Outcomes

For all analyses, the rate of change in eGFR over time was the primary outcome. For each patient, we calculated eGFR slope by fitting an ordinary least-squares regression line to all outpatient eGFR measures from T_0 until 30 September 2013. The slope of the regression line (β) describes the rate of change in kidney function (eGFR) over time. eGFR was calculated using the abbreviated 4-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on age, gender, race, and serum creatinine level.[28] Participants' eGFR was censored after the occurrence of ESRD, dialysis, or kidney transplant. All slopes required participants to have at least one eGFR that was $\geq$90 days from T_0. Rapid eGFR decline was defined as eGFR loss of $>$5 ml/min per 1.73 m^2/year, and stable eGFR decline was defined as eGFR loss of 0 to 1 ml/min per 1.73 m^2/year.[29]

Covariates

Baseline covariates were ascertained from 1 October 1999 until cohort entry (T_0 between 1 October 2002 and 30 September 2003). Covariates included age, race, gender, diabetes mellitus, and hypertension. Race and/or ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial and/or ethnic minority groups). Comorbidities were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and Current Procedural Terminology codes in the VA Medical SAS datasets.[11,30–32] Subjects were assigned geographic location based on their county information contained in the outpatient or inpatient data closest but prior to T_0. County-level variable data were obtained from the 2014 County Health Rankings national datasets.[26] We evaluated the relationship between rapid kidney function decline and county characteristics in 6 domains including health outcomes, health behaviors, clinical care, social and economic factors, physical environment, and demographics. Each domain represented a number of variables (Supplementary Table S1).[26] Only variables comparable across states were used in the analyses.[26]

Statistical Analysis

Rate of eGFR change per year was calculated using ordinary least squares. Crude prevalence of rapid eGFR decline (eGFR slope <-5 vs. eGFR slope ≥ -5) was computed as the number of subjects with outcome per 100 US veterans during follow-up. For adjusted measures of prevalence, mixed-effect logistic regression models were applied with covariates including age, race, gender, diabetes, and hypertension. A mixed model was used to account for potential intracorrelation within a county, and thus random intercepts with a compound symmetry covariance structure at the county level were fit. Covariate coefficients were first obtained from the mixed-effect logistic regression model and then the adjusted prevalence rates were calculated using the least-squared means method, where standardization was based on the national cohort's distribution of covariates. A Wald z test of the variance at the county level was used in assessing homogeneity at the county level.

Mixed models adjusted for age, race, and gender were additionally run in subsamples of those with and without diabetes, and with and without hypertension. Forest plots of adjusted prevalences are grouped by county quintiles, which represent those counties in the quintile of the age-, race-, and gender-adjusted prevalence in the overall cohort. Median, interquartile range, and confidence intervals (CI) of county prevalence in each quintile are shown.

To investigate ecologic predictors (odds ratio [OR]) of rapid eGFR decline, separate mixed models were built, where stable eGFR decline (eGFR loss of 0 to

−1 ml/min per 1.73 m^2/year) served as the reference category.[29]

Principal component analysis, a data reduction method that is often used when multicollinearity is of concern, was performed for each county variable domain. Principal component analysis produces unique components in descending order of explained variance of the variables entered into analysis based on the correlations between the variables. To aid interpretation, only the first component was retained.[33,34] The retained components were then used in mixed-effect logistics regression models to examine the relationship between county variable domain and eGFR decline. Factor loadings and percent variance explained by the first component are presented in Supplementary Table S2. Factor scores were computed and categorized at the county level in quartiles, where higher quartiles consisted of higher factor scores.

Cluster analysis was performed using the Cluster and Outlier Analysis tool in ArcMap, which uses the Anselin Local Moran's *I* statistics to test where there are geographic clusters of counties or outliers with prevalence that are higher or lower than the national average.[35] For the cluster analysis, the conceptualization of spatial relationships was inverse distance. The distance threshold used was the default threshold as calculated by the software algorithm, which is the minimum distance required so that all counties had at least one neighbor used in the calculations. Missing data were not imputed. In analyses, a 95% CI of an OR that does not include unity was considered statistically significant. In all analyses, a *P* value of 0.05 or less was considered statistically significant. All statistical analyses other than cluster analysis were done using SAS Enterprise Guide version 7.1 and SAS 9.4 (SAS Institute, Cary, NC). Geographic information system maps and cluster analysis were done using Arc Map 10 (ESRI, Redlands, CA).

Sensitivity Analysis

To test robustness of study findings, we undertook a number of sensitivity analyses where we additionally adjusted overall prevalence estimates, and estimates stratified by the presence of diabetes and hypertension, for initial eGFR. We also repeated prevalence analyses in a cohort restricted to participants from counties that contributed at least 210 participants to cohort. The number was derived from a power analysis to be able to detect prevalence from one half to twice the prevalence in the national cohort.

In spatial cluster analyses, we used distance thresholds that were 50% and 25% of the algorithm-generated distance threshold to assess robustness of clustering to spatial analysis parameter specifications; we repeated the analyses using initial eGFR as an additional covariate; and to assess the possible influence of counties with low number of participants on the cluster analyses, we performed the analyses only in counties that contributed at least 210 cohort participants (number generated by power analysis as described above).

RESULTS

There were 2,107,570 US veterans in the overall cohort: 169,029 (8.02%) with rapid eGFR decline defined as eGFR slope < -5 ml/min per 1.73 m^2/year, and 491,441 (23.32%) with stable eGFR (defined as eGFR slope 0 to −1 ml/min per 1.73 m^2/year and served as the reference group). The demographic and clinical characteristics of overall cohort and the rate of eGFR decline including those with stable and rapid eGFR slope are described in Table 1.

Rapid Kidney Function Decline and Geography

We categorized county-level prevalence of rapid eGFR decline in quintiles. Figure 2 depicts crude prevalence of rapid eGFR decline by county in the United States. Crude prevalence varied substantially from 0.0%–5.24% in the lowest quintile to 9.89%–36.84% in the highest quintile (*P* for heterogeneity < 0.001). For example, the crude prevalence was 4.45% in Garfield County, Colorado; 6.54% in Salt Lake County, Utah; 7.93% in Washington County, Maine; 9.32% in Los Angeles County, California; and 13.36% in Fulton County, Georgia. Adjusted prevalence for age, race, gender, diabetes, and hypertension (Figure 3) varied from 4.10%–6.72% in the lowest quintile to 8.41%–22.04% in the highest quintile (*P* for heterogeneity < 0.001). For example, the adjusted prevalence was 5.63% in Seminole County, Florida; 7.25% in Lancaster, Nebraska; 7.64% in Cass County, Texas; 8.39% in Chesapeake City, Virginia; and 11.85% in Wayne, Indiana. Adjusted prevalence stratified by status of diabetes (in those with and without diabetes) shows that prevalence was reduced but remained high and exhibited substantial geographic variation in those without diabetes (*P* for heterogeneity < 0.001) (Supplementary Figure S1). Similarly, there was substantial geographic variation in the adjusted prevalence of rapid eGFR decline in those with diabetes (*P* for heterogeneity < 0.001) (Supplementary Figure S2). Examination of adjusted prevalence by hypertension status (in those with and without hypertension) showed that the prevalence of rapid eGFR decline was decreased but also remained high with significant geographic variation in those without hypertension (*P* for heterogeneity < 0.001) (Supplementary Figure S3). Adjusted prevalence also varied significantly in those with hypertension (*P* for

Table 1. Demographic and clinical characteristics of overall study cohort and by rate of eGFR decline

	Overall N = 2,107,570	No eGFR decline Slope ≥0 (ml/min per 1.73 m^2/yr) N = 786,198 (37.30%)	Stable eGFR decline Slope <0 to −1 (ml/min per 1.73 m^2/yr) N = 491,441 (23.32%)	Mild eGFR decline Slope < −1 to −5 (ml/min per 1.73 m^2/yr) N = 660,902 (31.36%)	Rapid eGFR decline Slope < −5 (ml/min per 1.73 m^2/yr) N = 169,029 (8.02%)
Male (%)	2,009,962 (95.37)	744,617 (94.71)	469,052 (95.44)	633,751 (95.89)	162,542 (96.16)
Race (%)					
White	1,724,544 (81.83)	649,437 (82.60)	411,444 (83.72)	534,167 (80.82)	129,496 (76.61)
Black	307,910 (14.61)	108,301 (13.78)	61,916 (12.60)	104,454 (15.80)	33,239 (19.66)
Other	75,116 (3.56)	28,460 (3.62)	18,081 (3.68)	22,281 (3.37)	6294 (3.72)
Median age (yr) (IQR)	62.99 (54.47, 71.83)	61.15 (53.49, 71.01)	62.17 (54.20, 71.26)	64.78 (55.42, 72.59)	66.25 (56.17, 73.68)
Hypertension (%)	1,414,075 (67.10)	500,215 (63.62)	310,190 (63.12)	472,218 (71.45)	131,452 (77.77)
Diabetes (%)	595,561 (28.26)	175,798 (22.36)	114,365 (23.27)	226,005 (34.20)	79,393 (46.97)
Death during follow-up (%)	644,029 (30.56)	228,239 (29.03)	64,557 (19.24)	203,618 (30.81)	117,615 (69.58)
ESRD, dialysis, or kidney transplant during follow-up (%)	107,713 (5.11)	9856 (1.25)	7183 (1.46)	46,154 (6.98)	44,520 (26.34)
Average T_0 eGFR (ml/min per 1.73 m^2) (SD)	75.37 (19.47)	73.10 (18.00)	77.51 (19.37)	76.30 (20.20)	76.06 (22.17)
Average final eGFR (ml/min per 1.73 m^2) (SD)	69.26 (23.63)	80.70 (18.97)	72.93 (19.99)	59.14 (22.08)	44.93 (24.11)
Median slope (ml/min per 1.73 m^2/yr) (IQR)	−0.52 (−1.97, 0.59)	0.99 (0.44, 1.99)	−0.48 (−0.71, −0.25)	−2.08 (−2.10, −1.50)	−7.94 (−12.47, −6.07)
Median number of eGFR measurements (IQR)	14 (8, 22)	14 (8, 21)	15 (10, 22)	16 (9, 24)	8 (4, 16)
Median duration for eGFR slope (yr) (IQR)	9.28 (5.15, 10.00)	9.39 (5.25, 10.00)	9.72 (7.80, 10.08)	9.22 (5.64, 9.99)	2.81 (1.34, 5.23)
County-level characteristics[a]					
Health outcomes[b] (%)					
1—best	439,085 (24.57)	161,655 (24.29)	106,583 (25.80)	132,242 (23.51)	32,094 (22.03)
2	638,934 (35.76)	249,708 (37.52)	148,421 (35.93)	198,941 (35.37)	51,176 (35.13)
3	463,457 (25.94)	166,270 (24.98)	102,799 (24.89)	154,630 (27.49)	40,586 (27.86)
4—worst	245,248 (13.73)	87,970 (13.22)	55,259 (13.38)	76,587 (13.62)	21,803 (14.97)
Health behaviors[c] (%)					
1—best	650,907 (34.82)	233,700 (33.52)	155,318 (35.69)	208,943 (35.62)	52,946 (35.17)
2	615,564 (32.92)	238,227 (34.17)	141,898 (32.61)	187,191 (31.91)	48,248 (32.04)
3	407,178 (21.78)	150,781 (21.62)	92,444 (21.24)	130,568 (22.26)	33,385 (22.17)
4—worst	195,961 (10.48)	74,568 (10.69)	45,506 (10.46)	59,902 (10.21)	15,985 (10.62)
Clinical care[d] (%)					
1—best	626,639 (31.81)	231,723 (31.52)	152,746 (33.33)	193,799 (31.36)	48,371 (30.52)
2	555,242 (28.19)	200,082 (27.21)	127,454 (27.81)	181,029 (29.30)	46,677 (29.45)
3	459,572 (23.33)	173,127 (23.55)	104,417 (22.79)	144,387 (23.37)	37,641 (23.75)
4—worst	328,486 (16.67)	130,342 (17.73)	73,648 (16.07)	98,699 (15.97)	25,797 (16.28)
Social and economic factors[e] (%)					
1—best	415,670 (24.47)	151,348 (23.86)	101,304 (25.88)	131,300 (24.62)	31,718 (22.76)
2	488,958 (28.79)	189,613 (29.89)	112,329 (28.69)	148,280 (27.81)	38,736 (27.80)
3	551,557 (32.47)	207,075 (32.64)	123,644 (31.58)	174,215 (32.67)	46,623 (33.46)
4—worst	242,252 (14.26)	86,363 (13.61)	54,206 (13.85)	49,406 (14.89)	22,277 (15.99)
Physical environment[f] (%)					
1—best	429,499 (20.93)	184,289 (23.97)	101,868 (21.25)	140,519 (21.93)	33,851 (20.72)
2	591,192 (28.80)	222,340 (28.92)	139,967 (29.19)	170,849 (26.66)	43,747 (26.77)
3	666,692 (32.48)	228,538 (29.73)	154,182 (32.16)	190,057 (29.66)	53,771 (32.91)
4—worst	365,114 (17.79)	133,565 (17.37)	83,461 (17.41)	139,466 (21.76)	32,027 (19.60)
Demographics (%)					
1—lowest quartile	180,865 (8.58)	66,921 (8.51)	45,731 (9.31)	55,855 (8.45)	12,358 (7.31)
2	313,645 (14.88)	113,610 (14.45)	75,767 (15.42)	100,976 (15.28)	23,292 (13.78)
3	454,552 (21.57)	165,005 (20.99)	108,213 (22.02)	145,748 (22.05)	35,586 (21.05)
4—highest quartile	1,158,508 (54.97)	440,662 (56.05)	261,730 (53.26)	358,323 (54.22)	97,793 (57.86)

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IQR, interquartile range.
[a]Characteristics are the first component of principal component analysis in each category. Factor loadings can be found in Supplementary Table S2. Values 1–4 represent quartiles that we classified at the county level.
[b]Subcohort where data were available (n = 1,786,724).
[c]Subcohort where data were available (n = 1,869,610).
[d]Subcohort where data were available (n = 1,698,437).
[e]Subcohort where data were available (n = 2,052,497).
[f]Subcohort where data were available (n = 1,969,939).

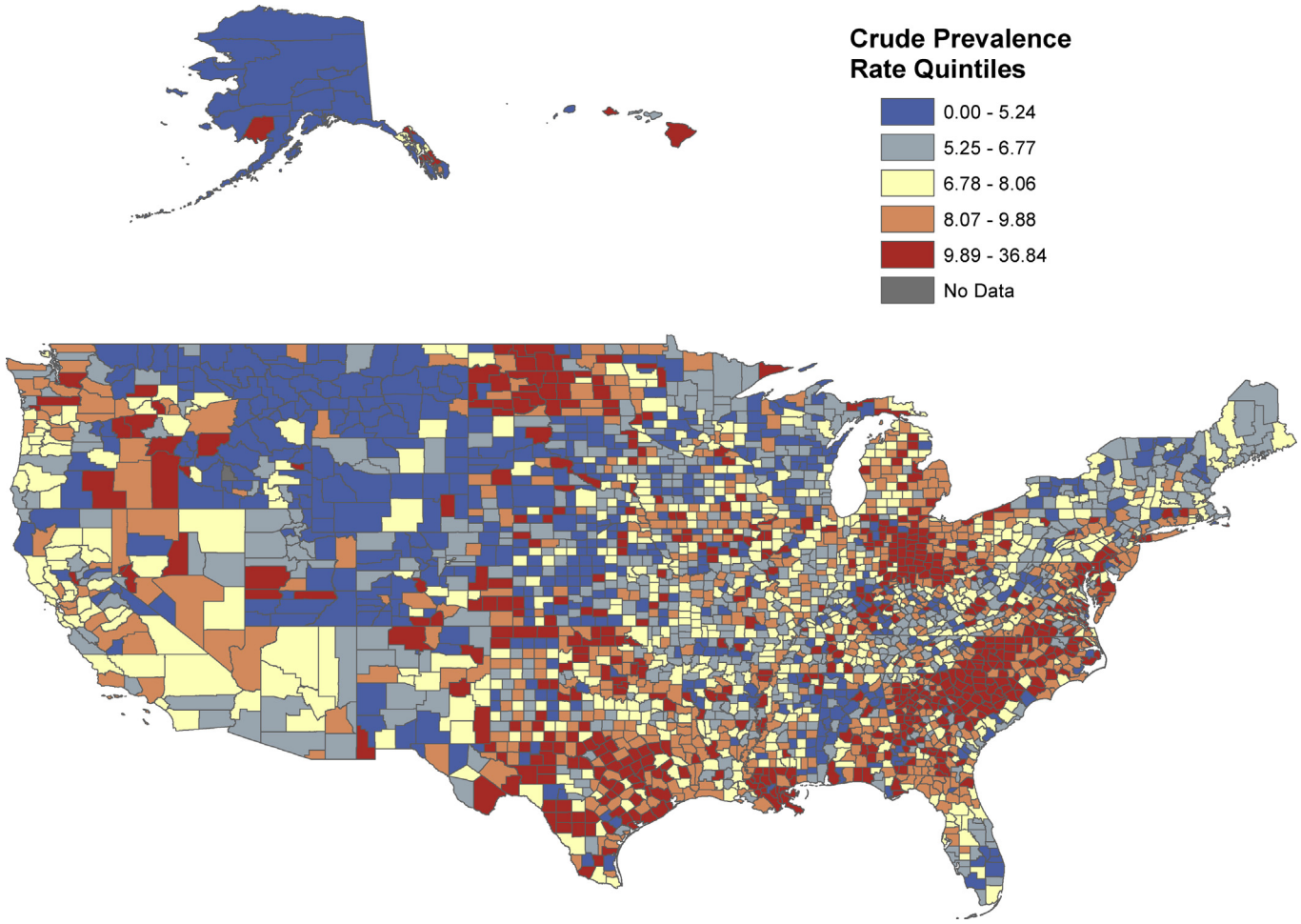

Figure 2. Crude prevalence of rapid estimated glomerular filtration rate decline. Prevalence represents number per 100 US veterans.

heterogeneity < 0.001) (Supplementary Figure S4). In quintiles categorized based on the age-, race-, and gender-adjusted prevalence of rapid eGFR decline, we examined the prevalence of rapid eGFR decline based on diabetes and hypertension status. The results show that within each quintile, the prevalence of rapid eGFR decline is much higher for those with diabetes and hypertension (Figure 4a and b). A comparison between quintiles in those with hypertension revealed that median-adjusted prevalence varied from 7.30% in quintile 1 to 10.24% in quintile 5, representing a 40.27% increase (Figure 4a). In those without hypertension, median-adjusted prevalence varied from 4.97% in quintile 1 to 6.40% in quintile 5, representing a 28.77% increase (Figure 4a). Median-adjusted prevalence varied from 11.69% to 14.14% (20.96% increase) in those with diabetes, and 4.70% to 6.85% (45.74% increase) in those without diabetes (Figure 4b), in quintiles 1 and 5, respectively.

Association Between US County Characteristics and Rapid eGFR Decline

In models adjusting for age, race, gender, diabetes, hypertension, and initial eGFR, we examined the association between rapid eGFR decline and county characteristics in 6 domains—whose values were obtained from the results of a principal component analysis and are provided in detail in Supplemental Table S2—including health outcomes, health behaviors, clinical care, social and economic factors, physical environment, and demographics. The relationship between eGFR decline and each domain is presented in Table 2. Results of the association between rapid eGFR decline and the variables in each domain are presented in Supplementary Table S2. Residents of counties that were in the worst quartile of health outcomes and health behaviors (quartile 4) had higher odds of rapid eGFR decline (OR = 1.15; CI = 1.09–1.22 and OR = 1.08; CI = 1.03–1.13, respectively) (Table 2). Residents living in counties where measures of access and quality of clinical care were poorest (quartile 4) had higher odds of rapid eGFR decline (OR = 1.11; CI = 1.06–1.16). Residents of counties with poorest social and economic conditions (quartile 4) had higher odds of rapid eGFR decline (OR = 1.15; CI = 1.09–1.22). Residents living in counties in worst physical environment quartile (quartile 4) were associated with higher odds of rapid eGFR decline (OR = 1.15; CI = 1.01–1.20).

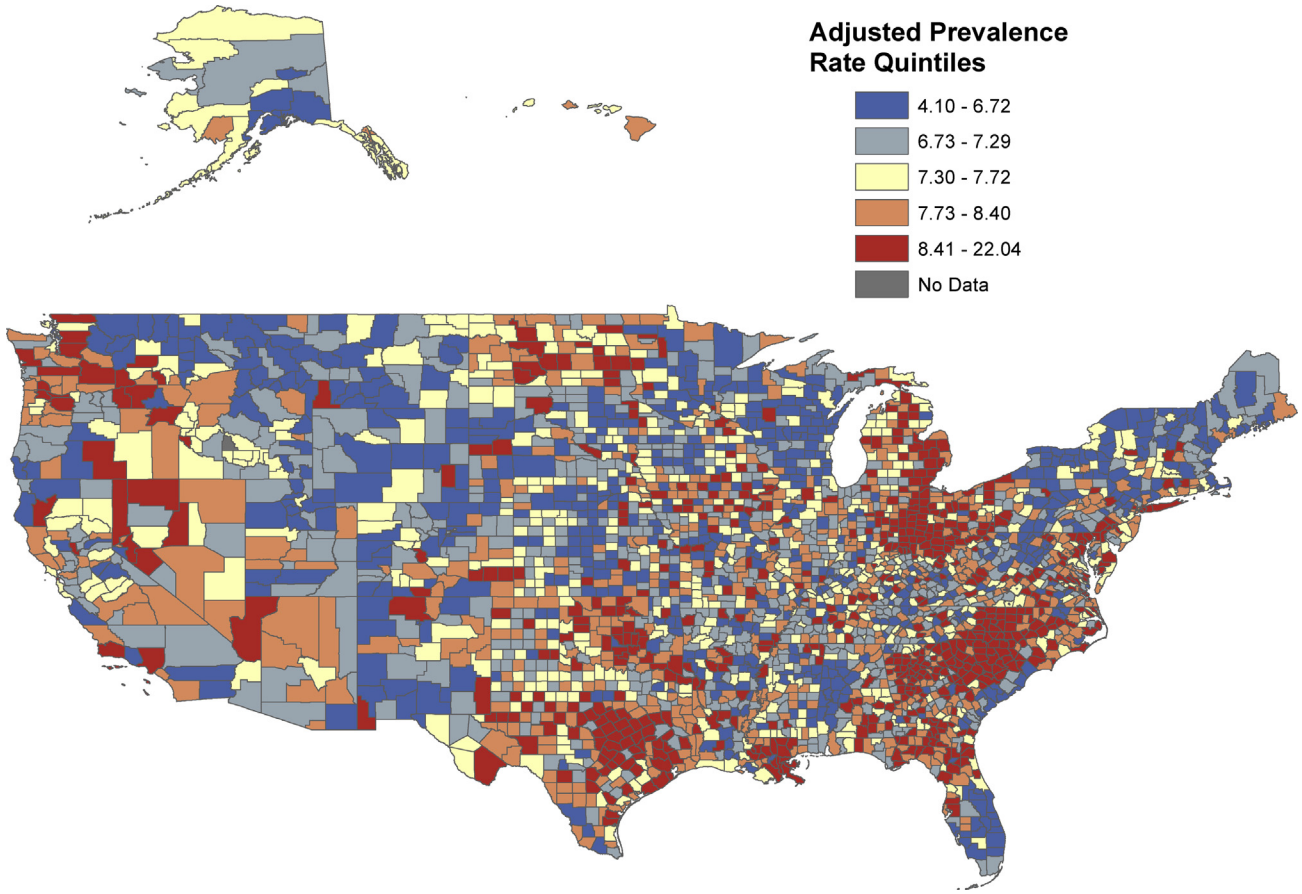

Figure 3. Adjusted prevalence of rapid estimated glomerular filtration rate decline. Adjusted for age, race, gender, diabetes, and hypertension. Prevalence represents number per 100 US veterans.

Residents living in counties with higher percentage of African Americans and other minorities, and communities with higher percentage of residents not proficient in English, were associated with higher odds of rapid eGFR decline (OR = 1.25; CI = 1.20–1.31).

In mixed-effect logistic regression models, we examined—as a measure of calibration—the association between individual-level predictors and rapid eGFR decline; the results were consistent with prior knowledge in that age, black race, diabetes, and hypertension were associated with increased odds of rapid eGFR decline (Supplementary Table S3).

Spatial Cluster Analysis

We undertook spatial cluster analysis, adjusting for age, race, gender, diabetes, and hypertension, to identify geographic areas with clusters of high prevalence of rapid eGFR decline beyond what is expected by random chance alone (Figure 5). Application of this analysis yielded clusters of high prevalence in the northwestern part of the USA including parts of Washington state; in the central southern part including much of Texas and Oklahoma; in the southeast including Alabama, Georgia, and the Carolinas; and the middle eastern part around Ohio. Low prevalence clusters were in the Middle West part of the USA, including Utah, Nebraska, and Wisconsin; the northeastern part including Maine and Vermont; and the southern tip of Florida.

Sensitivity Analyses

To test robustness of study findings, we examined the results in additional sensitivity analyses where (a) we additionally adjusted prevalence estimates for eGFR (Supplementary Figure S5) and examined differences in prevalence estimates by status of hypertension and diabetes after adjusting for eGFR (Supplementary Figure S6a and b); (b) we examined adjusted prevalence in a cohort restricted to participants from counties that contributed at least 210 participants to cohort (as described in the Methods section) (Supplementary Figure S7), and examined differences in prevalence estimates by status of hypertension and diabetes in this restricted cohort (Supplementary Figure S8a and b). The results were consistent with those shown in the primary analyses.

Spatial cluster analyses were repeated with various reduced distance thresholds, which introduced more stringent criteria for the detection of clustering, resulting in similar high prevalence clusters

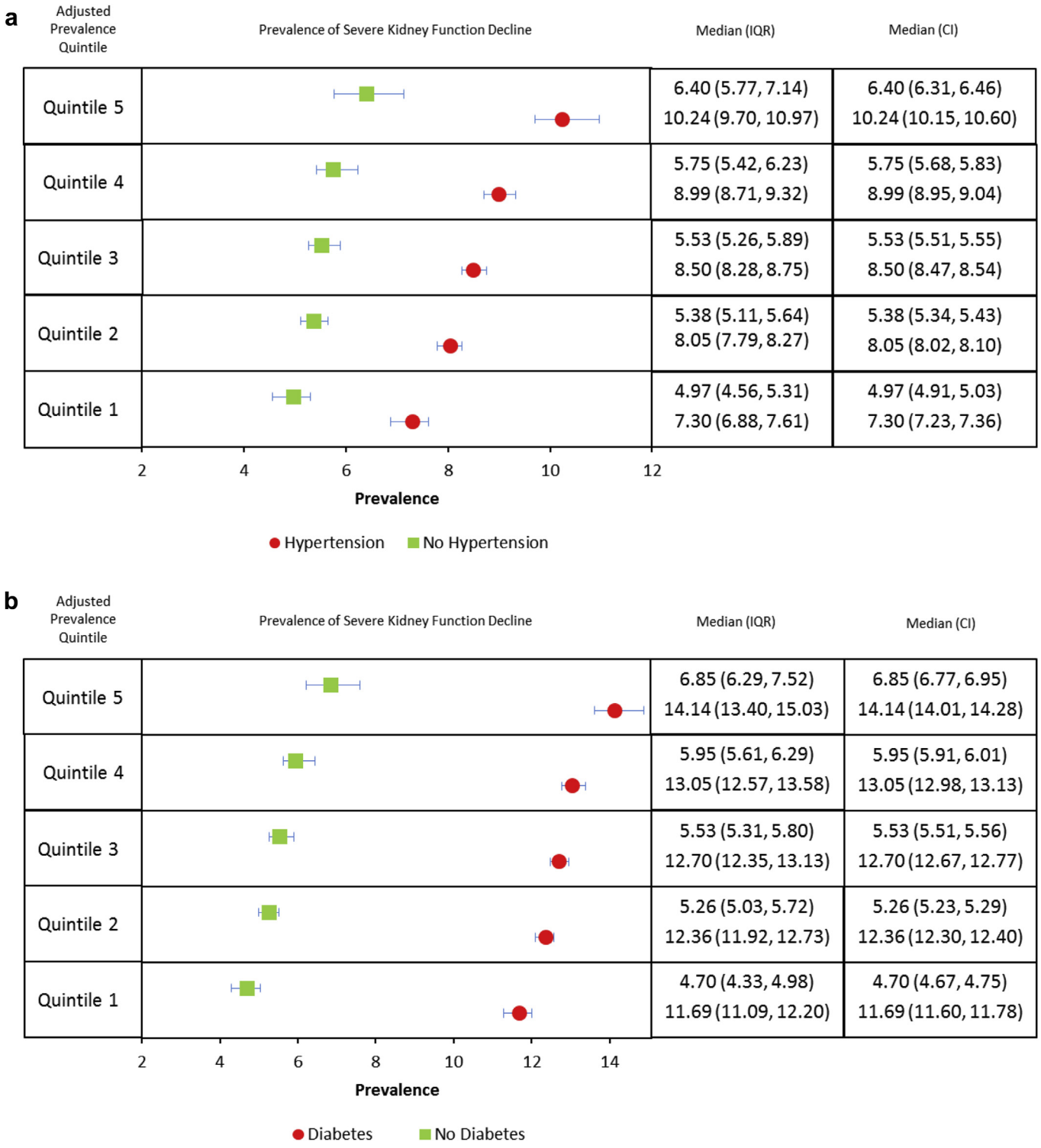

Figure 4. Median prevalence of rapid eGFR decline by (a) hypertension and (b) diabetes status. Adjusted for age, race, and gender. Prevalence represents number per 100 US veterans by disease status. Prevalence rates are grouped by county quintiles that are defined as the quintiles of age-, race-, and gender-adjusted prevalence in the overall cohort. Error bars represent IQR. CI, confidence interval; IQR, interquartile range.

(Supplementary Figure S9a and b). Low prevalence clusters also remained in the same areas. Cluster analyses that also included initial eGFR as a covariate yielded consistent results (Supplementary Figure S10). Spatial cluster analyses undertaken in a cohort were restricted to participants residing in counties that contributed at least 210 persons to cohort (as detailed in the Materials and Methods section), resulting in a similar pattern of clustering (Supplemental Figure S11).

Table 2. County characteristics and odds of rapid estimated glomerular filtration rate (eGFR) decline

Domain	N	Adjustment	Quartile 2 OR (CI)	Quartile 3 OR (CI)	Quartile 4 OR (CI)
Health outcomes	558,721	Unadjusted	1.15 (1.10, 1.21)	1.31 (1.24, 1.38)	1.26 (1.19, 1.33)
		Adjusted	1.11 (1.06, 1.17)	1.25 (1.19, 1.31)	1.15 (1.09, 1.22)
Health behaviors	585,730	Unadjusted	1.02 (0.97, 1.07)	1.14 (1.08, 1.20)	1.13 (1.07, 1.19)
		Adjusted	0.98 (0.94, 1.03)	1.10 (1.05, 1.15)	1.08 (1.03, 1.13)
Clinical care	616,751	Unadjusted	1.13 (1.08, 1.18)	1.21 (1.15, 1.27)	1.20 (1.15, 1.26)
		Adjusted	1.11 (1.06, 1.15)	1.15 (1.10, 1.20)	1.11 (1.06, 1.16)
Social and economic factors	530,837	Unadjusted	1.09 (1.03, 1.15)	1.18 (1.12, 1.25)	1.21 (1.14, 1.28)
		Adjusted	1.09 (1.03, 1.15)	1.14 (1.08, 1.21)	1.15 (1.09, 1.22)
Physical environment	642,874	Unadjusted	0.97 (0.93, 1.02)	1.07 (1.03, 1.12)	1.20 (1.15, 1.26)
		Adjusted	0.96 (0.92, 1.00)	1.02 (0.98, 1.07)	1.15 (1.01, 1.20)
Demographics	660,470	Unadjusted	1.14 (1.09, 1.19)	1.20 (1.15, 1.25)	1.32 (1.26, 1.37)
		Adjusted	1.12 (1.07, 1.17)	1.17 (1.12, 1.22)	1.25 (1.20, 1.31)

Quartile 1, which consisted of the lowest factor scores obtained from principal component analysis and represented the quartile with the most favorable domain conditions, served as the reference category.
Models adjusted for age, race, gender, diabetes, hypertension, and initial eGFR.
CI, confidence interval; OR, odds ratio.

DISCUSSION

Using VA national databases, we examined the geographic characteristics of rapid eGFR decline in the United States. Crude and adjusted prevalence vary substantially by geography. Diabetes and hypertension are major drivers of rapid eGFR decline, but analyses adjusting for those drivers still yielded substantial geographic variation in the prevalence of rapid eGFR decline. There was a significant relationship between rapid eGFR decline and characteristics of US counties in domains including health outcomes,

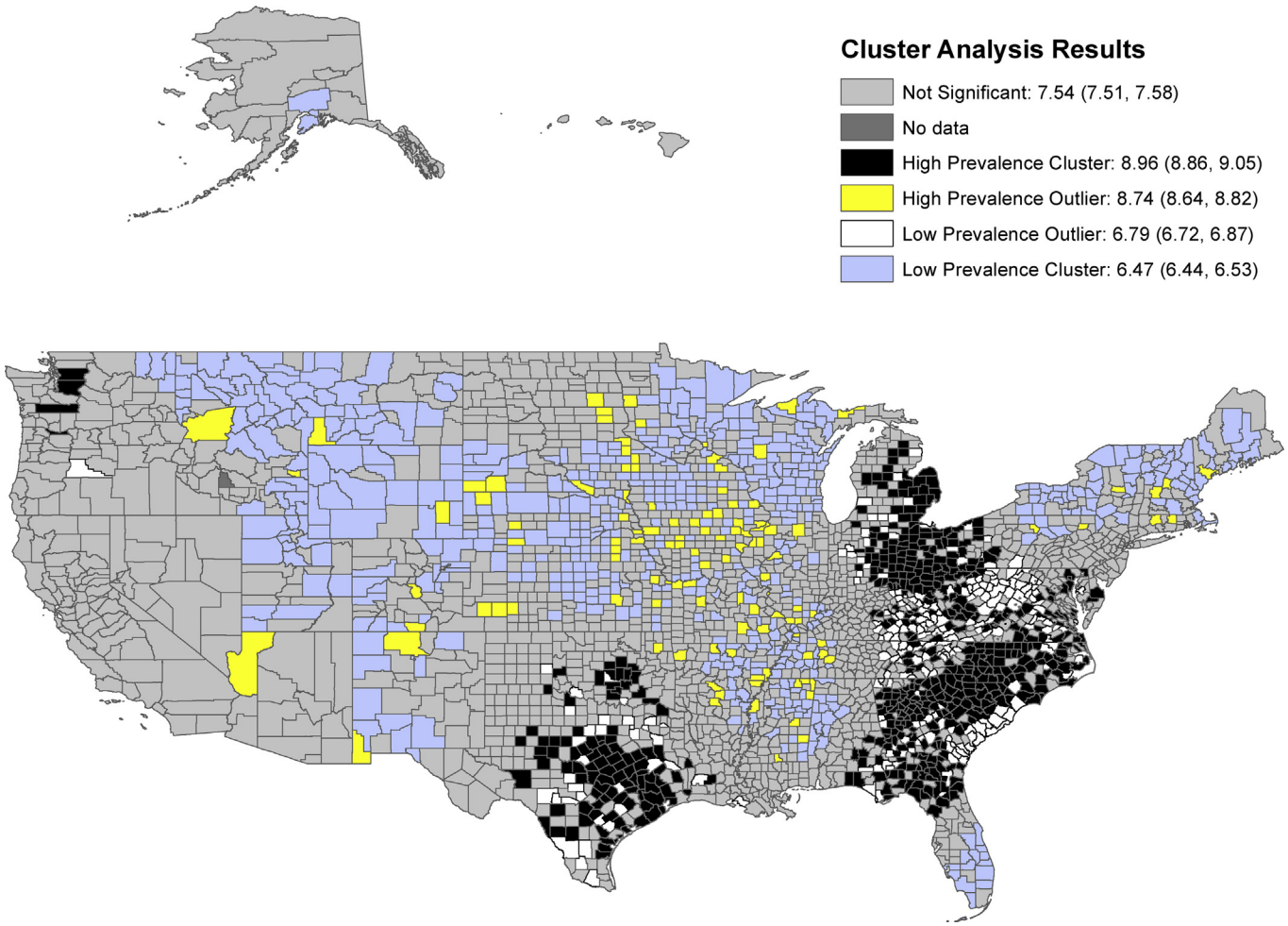

Figure 5. Geographic clustering of rapid estimated glomerular filtration rate decline prevalence. Adjusted for age, race, gender, diabetes, and hypertension. Median (confidence interval) prevalence represents number per 100 US veterans.

health behaviors, clinical care, social and economic factors, physical environment, and demographics. Spatial cluster analysis suggests the presence of geographic areas with high prevalence of rapid eGFR decline, and areas with low prevalence of rapid eGFR decline.

The analysis capitalized on the fact that the national VA health care system is centrally operated and to a large extent guided by uniform set of policies and procedures and evenly applied resource allocation methods where eligible veterans theoretically have access to the same care everywhere. Despite this, our analysis shows substantial geographic heterogeneity even after adjusting for demographics and major drivers of disease progression. The constellation of findings suggests a significant relationship between geographic or neighborhood factors and rapid eGFR decline. Occelli *et al*.[36] examined the spatial disparities in the incidence of ESRD in the Nord-Pas-de-Calais region in northern France—a region characterized by high population density and homogeneous health care provision—and found significant spatial disparities in gender- and age-adjusted ESRD incident ratios that were not explained by early dialysis initiation and strongly correlated with measures of economic deprivation. Hao *et al*.[17] examined geographic variation in rates of pre-ESRD care and observed that dialysis facilities with the lowest pre-ESRD care were more likely to be located in urban counties with high African American populations and low educational attainment. Yan *et al*.[19] examined variation in receiving pre-ESRD care and black-white disparities and reported that large metropolitan and rural counties had lower percentages of patients who received pre-ESRD nephrology care, and that regardless of geography black patients received less care than their white counterparts. Further analyses showed that state socioeconomic characteristics impact the likelihood of the receipt of predialysis nephrologist care.[18] In our analyses, geographic attributes and US county characteristics in domains capturing social, economic conditions, physical environment, demographic characteristics of diversity and inclusion, and measures of quality and outcomes of care in communities were associated with odds of rapid eGFR decline; our findings further expand on the existing body of evidence and specifically establishes an association between characteristics of US counties and rapid eGFR decline. The results further emphasize the notion that among US veterans receiving care at the same health care system, and where we also adjusted for individual-level risk factors for kidney disease progression, local geographic and neighborhood factors remain important drivers of health outcomes including rapid eGFR decline and that the health of communities where people live matters to individual health.

It is not clear why geographic variation in the prevalence of rapid eGFR decline exists. Heterogeneity or differences in dietary habits, protein intake, physical activity, smoking rates, and local neighborhood factors that include availability of parks, recreational space, and public infrastructure to promote physical activity might explain some of the variation. It is also likely that environmental or occupational factors, variation in the use of analgesics, and variation in exposure to heavy metals might affect the prevalence of rapid eGFR decline. It is also plausible that there might be local or regional variation in care practices and access to care (primary or specialty care) that might explain some of the variation observed in this report. Gene-neighborhood interactions may explain some of the variations seen; genetic polymorphism associated with higher risk of rapid eGFR decline may not be geographically randomly distributed and may be regionally concentrated in areas where we identified clustering of rapid eGFR decline.

The spatial cluster analyses in this report suggest the presence of areas of high prevalence of rapid eGFR decline. The areas identified were in the state of Texas, and the southeastern United States. It is not clear what factors (geographic or other) are responsible for these clusters, and it is not clear whether these same clusters exist among non-VA patients. Zarkowsky *et al*. examined the presence of incident functional arteriovenous fistula in a cohort of 464,547 patients beginning hemodialysis, and found marked regional variation in incident functional arteriovenous fistula, and risk-adjusted ESRD mortality among ESRD networks where the networks representing Texas and other areas in the American South had the lowest percentage in incident arteriovenous fistula and highest mortality risk.[37] Furthermore, analyses by Yan *et al*. showed that Middle Atlantic and Southern states exhibited lower than average probability of receipt of pre-ESRD nephrology care;[18,19] interestingly, these areas correspond to some of the clusters identified in our report. Further examination of these high prevalence clusters is needed to develop a better understanding of the geographic determinants of higher prevalence of rapid eGFR decline.

Our study has a number of limitations. The cohort included mostly older white male US veterans; thus, the results may not be generalizable to less narrowly defined populations. The imperfect nature of administrative data and the retrospective design of the study may also lead to sampling bias and inaccurate measurements or misclassification of the predictor variables. To reduce such measurement bias, we used definitions of comorbid illnesses that are validated for use in VA administrative data.[30–32] Cohort inclusion criteria may have resulted in selection bias; although serum creatinine is a routinely

measured laboratory parameter, this nevertheless requires interfacing with the VA health care system, the likelihood (or probability) of which may be higher in people with less optimal health. Although the analyses were adjusted for major drivers of kidney disease progression including age, race, gender, diabetes, hypertension, and eGFR, it is possible that residual confounding from unmeasured or unknown confounders may explain the observed variations. Our datasets did not include information on smoking and obesity; both are risk factors for eGFR decline and exhibit substantial geographic variation. Residential county was treated as static, and our analyses did not factor in change in patient residence that may have occurred over time. County-level characteristics data were obtained from the 2014 County Health Rankings dataset, and may not accurately reflect these characteristics during our baseline period of fiscal year 2003. County-level data were variably missing for several counties, which could have resulted in a selection bias. Effect sizes (OR) are modest, and because of the very large sample size statistical significance should be interpreted with caution. However, in ecologic research point estimates are often very modest, but interpreted as meaningful and impactful in terms of public health relevance due to the large amount of people affected in the studied ecologies.[17]

The aim of this study was to characterize the spatial epidemiology of rapid eGFR decline among users of the VA health care system and the results do not represent the epidemiology of fast eGFR decline in the United States; however, the results shed some light in that they show substantial geographic variation in rapid eGFR decline among users of a national integrated network of health care systems designed to reduce disparities and variation in health practices. The results showing that neighborhood factors and geography still matter substantially among users of the same integrated health care system further emphasize the importance of taking these factors into account in considering allocation of health care resources, design, planning, and implementation of programs and initiatives to reduce disparities, and in the study of factors that influence human health and disease in general. Most importantly, our study provides a framework for the examination of the spatial epidemiology of longitudinal parameters (eGFR slope in this report) and illustrates that beyond the examination of cross-sectional measures of CKD and ESRD epidemiology, the spatial epidemiology of longitudinal eGFR change over time provides important insight to enhance our understanding of geographic factors that might drive faster progression, and in informing targeted intervention for areas with high prevalence of rapid eGFR decline.

Black and van der Veer[38] draw on the Darwinian philosophy and note that describing and studying variation will unlock a better understanding of disease, and mechanisms of change. In the era of precision medicine—largely enabled by significant advances in biotechnology—where much attention is being devoted to individual-level characteristics that drive health outcomes, it is important to remain cognizant that ecologic conditions including social, economic, and environmental health of communities matters to health of individuals.[39] System-level factors, and geographic and neighborhood characteristics—the study of which is also enabled by a parallel evolution in data science (and the growing repertoire of routinely collected electronic health information), geographic information systems, and analytics—are also important in shaping health outcomes.[40–42] Attention to these parameters in precision public health will certainly advance our understanding of the ecologic determinants of health and disease and serve to promote public health.[16,39–48]

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Support for VA/Centers for Medicare and Medicaid Services data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Number/Data Use Agreement ID AI-Aly-01). This work was funded by a grant from the US Department of Veterans Affairs (for ZA-A). The contents do not represent the views of the US Department of Veterans Affairs or the US Government.

SUPPLEMENTARY MATERIAL

Figure S1. Adjusted prevalence of rapid eGFR decline in those without diabetes. Adjusted for age, race, and gender. Prevalence represents number per 100 US veterans.

Figure S2. Adjusted prevalence of rapid eGFR decline in those with diabetes. Adjusted for age, race, and gender. Prevalence represents number per 100 US veterans.

Figure S3. Adjusted prevalence of rapid eGFR decline in those without hypertension. Adjusted for age, race, and gender. Prevalence represents number per 100 US veterans.

Figure S4. Adjusted prevalence of rapid eGFR decline in those with hypertension. Adjusted for age, race, and gender. Prevalence represents number per 100 US veterans.

Figure S5. eGFR adjusted prevalence of rapid eGFR decline. Adjusted for age, race, gender, diabetes, hypertension, and eGFR. Prevalence represents number per 100 US veterans.

Figure S6. Median eGFR adjusted prevalence of rapid eGFR decline by (a) hypertension and (b) diabetes status. Adjusted for age, race, gender, and eGFR. Prevalence represents number per 100 US veterans. Quintiles are defined as the quintiles of age, race, and gender adjusted prevalence in the overall cohort. Error bars represent IQR.

Figure S7. Adjusted prevalence of rapid eGFR decline in a cohort with required n $\geq$ 210. Adjusted for age, race, gender, diabetes, and hypertension. Prevalence represents number per 100 US veterans.

Figure S8. Median adjusted prevalence of rapid eGFR decline by (a) hypertension and (b) diabetes status in a cohort with required n $\geq$ 210. Adjusted for age, race, gender, and eGFR. Prevalence represents number per 100 US veterans. Quintiles are defined as the quintiles of age, race, and gender adjusted prevalence in the overall cohort. Error bars represent IQR.

Figure S9. Geographic clustering of rapid eGFR decline prevalence with (a) 50% and (b) 25% original distance threshold. Adjusted for age, race, gender, diabetes, and hypertension. Median (CI) prevalence represents number per 100 US veterans.

Figure S10. eGFR adjusted cluster analysis of rapid eGFR decline prevalence. Adjusted for age, race, gender, diabetes, hypertension, and eGFR. Median (CI) prevalence represents number per 100 US veterans.

Figure S11. Geographic clustering of eGFR decline prevalence in a cohort with required n $\geq$ 210. Adjusted for age, race, gender, diabetes, and hypertension. Median (CI) prevalence represents number per 100 US veterans.

Table S1. County characteristics variable definitions, data sources, and values.

Table S2. County characteristics and odds of rapid eGFR decline. County characteristics were evaluated in 6 domains including health outcomes, health behaviors, clinical care, social and economic factors, physical environment, and demographics.

Table S3. Individual-level predictors of rapid eGFR decline. Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Rodriguez RA, Hotchkiss JR, O'Hare AM. Geographic information systems and chronic kidney disease: racial disparities, rural residence and forecasting. *J Nephrol*. 2013;26:3–15.
2. McClellan AC, Plantinga L, McClellan WM. Epidemiology, geography and chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2012;21:323–328.
3. Toubiana L, Richard JB, Landais P. Geographical information system for end-stage renal disease: SIGNe, an aid to public health decision making. *Nephrol Dial Transpl*. 2005;20:273–277.
4. Tanner RM, Gutierrez OM, Judd S, et al. Geographic variation in CKD prevalence and ESRD incidence in the United States: results from the reasons for geographic and racial differences in stroke (REGARDS) study. *Am J Kidney Dis*. 2013;61:395–403.
5. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*. 2015;88:950–957.
6. Brück K, Stel VS, Gambaro G, et al. CKD prevalence varies across the European General Population. *J Am Soc Nephrol*. 2016;27:2135–2147.
7. Al-Aly Z, Zeringue A, Fu J, et al. Rate of kidney function decline associates with mortality. *J Am Soc Nephrol*. 2010;21:1961–1969.
8. Kovesdy CP, Coresh J, Ballew SH, et al. Past decline versus current eGFR and subsequent ESRD risk. *J Am Soc Nephrol*. 2016;27:2447–2455.
9. Naimark DM, Grams ME, Matsushita K, et al. Past decline versus current eGFR and subsequent mortality risk. *J Am Soc Nephrol*. 2016;27:2456–2466.
10. Xie Y, Bowe B, Xian H, et al. Rate of kidney function decline and risk of hospitalizations in stage 3A CKD. *Clin J Am Soc Nephrol*. 2015;10:1946–1955.
11. Al-Aly Z, Balasubramanian S, McDonald JR, et al. Greater variability in kidney function is associated with an increased risk of death. *Kidney Int*. 2012;82:1208–1214.
12. Xie Y, Bowe B, Xian H, et al. Renal function trajectories in patients with prior improved eGFR slopes and risk of death. *PLoS One*. 2016;11:e0149283.
13. Xie Y, Bowe B, Xian H, et al. Estimated GFR trajectories of people entering CKD stage 4 and subsequent kidney disease outcomes and mortality. *Am J Kidney Dis*. 2016;68:219–228.
14. Al-Aly Z. Prediction of renal end points in chronic kidney disease. *Kidney Int*. 2013;83:189–191.
15. Al-Aly Z, Cepeda O. Rate of change in kidney function and the risk of death: the case for incorporating the rate of kidney function decline into the CKD staging system. *Nephron Clin Pract*. 2011;119:c179–c185 [discussion c186].
16. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol*. 2016;27:2576–2595.
17. Hao H, Lovasik BP, Pastan SO, et al. Geographic variation and neighborhood factors are associated with low rates of pre-end-stage renal disease nephrology care. *Kidney Int*. 2015;88:614–621.
18. Yan G, Cheung AK, Greene T, et al. Interstate variation in receipt of nephrologist care in US patients approaching ESRD: race, age, and state characteristics. *Clin J Am Soc Nephrol*. 2015;10:1979–1988.
19. Yan G, Cheung AK, Ma JZ, et al. The associations between race and geographic area and quality-of-care indicators in patients approaching ESRD. *Clin J Am Soc Nephrol*. 2013;8:610–618.
20. Murphy PA, Cowper DC, Seppala G, et al. Veterans Health Administration inpatient and outpatient care data: an overview. *Eff Clin Pract*. 2002;5:E4.
21. Oddone EZ, Eisen S. Veterans Affairs Research and Development: using science to improve health care for veterans. *North Carolina Med J*. 2008;69:35–37.

22. *VIReC Research User Guide: VHA Medical SAS® Outpatient Datasets FY2006*. Hines, IL: US Department of Veterans Affairs. VA Information Resource Center; September 2007.
23. *VIReC Research User Guide: VHA Medical SAS® Inpatient Datasets FY2006*. Hines, IL: US Department of Veterans Affairs. VA Information Resource Center; September 2007.
24. *VIReC Research User Guide: Veterans Health Administration Decision Support System Clinical National Data Extracts*. Hines, IL: US Department of Veterans Affairs. VA. Information Resource Center; September 2009.
25. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*. 2016;67:A7–A8.
26. Remington PL, Catlin BB, Gennuso KP. The County Health Rankings: rationale and methods. *Popul Health Metr*. 2015;13:11.
27. Robert Wood Johnson Foundation, County Health Rankings & Roadmaps. Available at: http://www.countyhealthrankings.org/rankings/data. Accessed August 17, 2016.
28. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
29. Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney Int Suppl*. 2013;3:63–72.
30. Bowe B, Xie Y, Xian H, et al. Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression. *Kidney Int*. 2016;89:886–896.
31. Bowe B, Xie Y, Xian H, et al. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. veterans [e-pub ahead of print]. Clin J Am Soc Nephrol. pii: CJN.00730116. Accessed August 31, 2016.
32. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol*. 2016;27:3153–3163.
33. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health*. 2006;83:1041–1062.
34. Singh GK. Area deprivation and widening inequalities in US mortality, 1969–1998. *Am J Public Health*. 2003;93:1137–1143.
35. Anselin L. Local indicators of spatial association—LISA. *Geographical Analysis*. 1995;27:93–115.
36. Occelli F, Deram A, Genin M, et al. Mapping end-stage renal disease (ESRD): spatial variations on small area level in northern France, and association with deprivation. *PLoS One*. 2014;9:e110132.
37. Zarkowsky DS, Hicks CW, Arhuidese I, et al. Quality improvement targets for regional variation in surgical end-stage renal disease care. *JAMA Surg*. 2015;150:764–770.
38. Black C, van der Veer SN. Unlocking the value of variation in CKD prevalence. *J Am Soc Nephrol*. 2016;27:1874–1877.
39. Greer S, Schieb LJ, Ritchey M, et al. County health factors associated with avoidable deaths from cardiovascular disease in the United States, 2006–2010. *Public Health Rep*. 2016;131:438–448.
40. Khoury MJ, Iademarco MF, Riley WT. Precision public health for the era of precision Medicine. *Am J Prev Med*. 2016;50:398–401.
41. Bayer R, Galea S. Public health in the precision-medicine era. *N Engl J Med*. 2015;373:499–501.
42. Khoury MJ, Evans JP. A public health perspective on a national precision medicine cohort: balancing long-term knowledge generation with early health benefit. *JAMA*. 2015;313:2117–2118.
43. Ainsworth J, Buchan I. Combining health data uses to ignite health system learning. *Methods Inf Med*. 2015;54:479–487.
44. Bello A, Hemmelgarn B, Manns B, et al. Use of administrative databases for health-care planning in CKD. *Nephrol Dial Transpl*. 2012;27(suppl 3):iii12–iii18.
45. Bello AK, Levin A, Manns BJ, et al. Effective CKD care in European countries: challenges and opportunities for health policy. *Am J Kidney Dis*. 2015;65:15–25.
46. Norris K, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the United States. *J Am Soc Nephrol*. 2008;19:1261–1270.
47. Nicholas SB, Kalantar-Zadeh K, Norris KC. Racial disparities in kidney disease outcomes. *Semin Nephrol*. 2013;33:409–415.
48. Crews DC, Pfaff T, Powe NR. Socioeconomic factors and racial disparities in kidney disease outcomes. *Semin Nephrol*. 2013;33:468–475.