Disease-specific incident glomerulonephritis displays geographic clustering in under-serviced rural areas of British Columbia, Canada

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There is little known about geographic variability in the incidence of glomerular disease and its potential implications for care delivery. To evaluate this, we performed a population-level cohort study using a provincial renal pathology database (2000-2012) to capture all incident cases of glomerulonephritis in British Columbia, Canada. This included 401 patients with membranous nephropathy (MN), 824 patients with IgA nephropathy (IgAN), 385 patients with focal segmental glomerulosclerosis (FSGS), 397 patients with lupus nephritis (LN) and 399 patients with ANCA-related glomerulonephritis (ANCA-GN). Geographic clusters were identified using Bayesian spatial models to estimate the incidence of each disease in 74 regions compared to the mean incidence in the entire province (incidence rate ratio, [IRR]), adjusted for region-level age, sex and race. The proportion of overall variability in incidence attributed to inter-regional differences varied by disease: 18% in MN, 81% in IgAN, 18% in FSGS, 59% in ANCA-GN, and 89% in LN. Except for LN, clustering was not explained by demographics. All IgAN and LN clusters were in urban regions close to nephrology centers, whereas ANCA-GN, MN and FSGS clustered mainly in rural regions. All ANCA-GN clusters were rural with median population density 1.2 persons/km^2 and driving distances of 10-676 km to the nearest nephrology center. Thus, we found significant geographic clustering in the incidence of different glomerular diseases. MN, FSGS and ANCA-GN clustered in sparsely populated regions with limited access to care, underscoring the importance of regional variability in glomerular diseases to inform health services delivery.

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There is a paucity of literature describing the epidemiology of glomerular diseases. Prior studies have relied on local biopsy or end-stage kidney disease (ESKD) registries for which the source populations are unclear.[1] Thus, the true incidence of glomerular diseases at the time of onset, including geographic variation in disease, is largely unknown.[2] The accurate measurement of disease incidence is important for several reasons. First, glomerular diseases are a significant public health challenge. Although individual diseases are considered to be rare, they collectively account for approximately 20% of the prevalent ESKD population in Canada.[3] In addition to a high risk of disease progression, the burden of glomerular disease on individual patients, their families, and the health care system is considerable owing to toxicity of current treatments, increased hospitalization rates, loss of earning potential and high costs associated with novel immune therapies.[4–7] Understanding the implications of these factors for health care–system planning is not possible without an accurate assessment of the incidence of disease. Second, the management of glomerular disease is often complex, requiring highly specialized nephrology care and frequent monitoring. Understanding who is at risk of developing glomerular disease is therefore essential to ensure that care is optimal and resources can be delivered to those who need them. Finally, although recent studies have provided a granular understanding of the molecular basis of distinct disease subtypes,[8–13] the factors that ultimately drive disease onset have not been delineated to the same degree. Well conducted epidemiologic studies in glomerular disease are needed to identify subpopulations at higher risk of disease and generate hypotheses regarding pathogenesis.

Population-level disease surveillance can provide a better understanding of the incidence of disease, and its relationship to geography and access to care. For example, a well established finding is that certain disadvantaged populations have a higher prevalence of undifferentiated chronic kidney disease, especially those living in remote areas with poor access to health care resources.[14,15] Such disparity would be particularly challenging in glomerular disease, the diagnosis and management of which requires timely access to a nephrologist and kidney biopsy, frequent clinical and laboratory

monitoring, especially during periods of intense immunosuppression, and access to newer targeted therapies that are expensive and often require specific expertise. Therefore, the allocation and delivery of such specialized health care resources requires a detailed understanding of the population-level geographic distribution of disease. In the absence of good-quality epidemiologic data, whether underserviced populations are at higher risk of developing glomerular disease is unknown, along with whether they have the necessary access to optimal care for prevention of disease progression.

We hypothesized that glomerular disease subtypes exhibit disease-specific geographic clustering of incident cases, with potential implications for the optimal delivery of specialized nephrology care. To investigate this possibility, we employed a Bayesian spatial model to identify geographic clusters of disease subtypes in a large and multiethnic Canadian province, using a centralized biopsy registry and demographic data from an accurately defined source population.

RESULTS

A total of 2406 patients were included: 401 with membranous nephropathy (MN), 824 with IgA nephropathy (IgAN), 385 with focal segmental glomerulosclerosis (FSGS), 399 with antineutrophil cytoplasm antibody–related glomerulonephritis (ANCA-GN), and 397 with lupus nephritis (LN). Demographic and clinical characteristics of the specific glomerular disease cohorts are detailed in Table 1. As expected, patients with LN and IgAN tended to be younger and were more commonly of Asian origin, whereas patients with MN, ANCA-GN, and FSGS were most commonly Caucasian. A substantial proportion (17%) of ANCA-GN patients were Aboriginal. Patients with ANCA-GN had the lowest estimated glomerular filtration rate at the time of biopsy, and patients with MN had the greatest degree of proteinuria. A description of the population of British Columbia (BC) and distributions of age, sex, and race are provided in Supplementary Table S1. The overall crude incidence rate (per 100,000 person-years) was 1.79 (95% confidence interval [CI] 1.66–1.91) for IgAN, 0.87 (95% CI 0.78–0.95) for MN, 0.83 (95% CI 0.75–0.91) for FSGS, 0.86 (95% CI 0.78–0.95) for LN, and 0.86 (95% CI 0.78–0.95) for ANCA-GN.

Identification of geographic clusters

In a model with no covariates, the proportion of overall variability in the incidence of disease that was attributable to interregional differences varied substantially by type of glomerular disease: 18% in MN, 81% in IgAN, 18% in FSGS, 59% in ANCA-GN, and 89% in LN (Supplementary Table S2). Univariable analyses identified disease-specific measures of region-level age, sex, and race that conferred higher risk (Supplementary Table S3). Using these disease-specific covariates, we generated models for each type of glomerular disease that identified potential geographic clusters (Figure 1). Prominent geographic clusters were found for IgAN (incidence rate ratio [IRR] range 1.27–1.94), MN (IRR range 1.13–1.45), FSGS (IRR range 1.22–1.61), ANCA-GN (IRR range 1.19–3.53), and LN (IRR range 1.46–2.58). The location of clusters varied by type of disease. All the glomerular disease subtypes except ANCA-GN had different clusters in the southwestern corner of the province near the region's major urban center (the city of Vancouver). MN, FSGS, and ANCA-GN had additional clusters in rural regions. This clustering was most prominent for ANCA-GN and

Table 1 | Patient characteristics for each glomerulonephritis subtype at the time of kidney biopsy

Characteristic	MN	IgAN	ANCA-GN	LN	FSGS
N	401	824	399	397	385
Age (yr)	56 (16)	44 (15)	61 (17)	35 (14)	49 (20)
Male sex	57	61	45	17	57
Race					
Caucasian	45.9	34.4	53.2	17.2	51
Black	0.4	0.2	0	1.7	3
Asian	24.9	47.7	16.5	59.5	21
South Asian	22.3	11.5	8.6	13.1	14
Aboriginal	4.7	3.5	17.9	3.8	6
Latin American	0.4	1.2	0.8	1.1	1
Arabian	1.3	1.2	0.8	2.1	3
Other	0	0.3	2.3	1.4	1
Creatinine (umol/l)	90 [71–127]	122 [90–193]	273 [181–417]	84 [61–130]	150 [90–227]
eGFR (ml/min per 1.73 m^2)	76 [46–96]	54 [30–80]	17 [10–29]	93 [83–107]	40 [22–69]
MAP (mm Hg)	97.4 (14.8)	100.7 (15.3)	94.8 (15)	95.7 (16.8)	100.7 (17.2)
Albumin (g/l)	26.2 (8)	36.7 (6.5)	31.7 (6.6)	30.1 (8.2)	33 (8.7)
Proteinuria (g/d)	5.8 [3.4–8.8]	1.7 [0.9–3.2]	1.2 [0.6–2.2]	2.1 [1.1–3.9]	3 [1.6–6.0]
Progression to ESKD	13	28	30	14	35
Incidence rate (per 100,000 person-years)	0.87 (0.78–0.95)	1.79 (1.66–1.91)	0.86 (0.78–0.95)	0.86 (0.78–0.95)	0.83 (0.75–0.91)

ANCA-GN, anti-neutrophil cytoplasm antibody–related glomerulonephritis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MAP, mean arterial pressure; MN, membranous nephropathy.
Values given are mean (SD), median (interquartile range), or percentage, unless otherwise indicated.
Laboratory data and blood pressure were taken as the closest values within 6 months of the biopsy from either the British Columbia Renal Agency or pathology databases.
Daily protein excretion was measured by 24-hour urine collection, or estimated from urine albumin-to-creatinine and protein-to-creatinine ratios.
GFR was estimated from provincially standardized creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

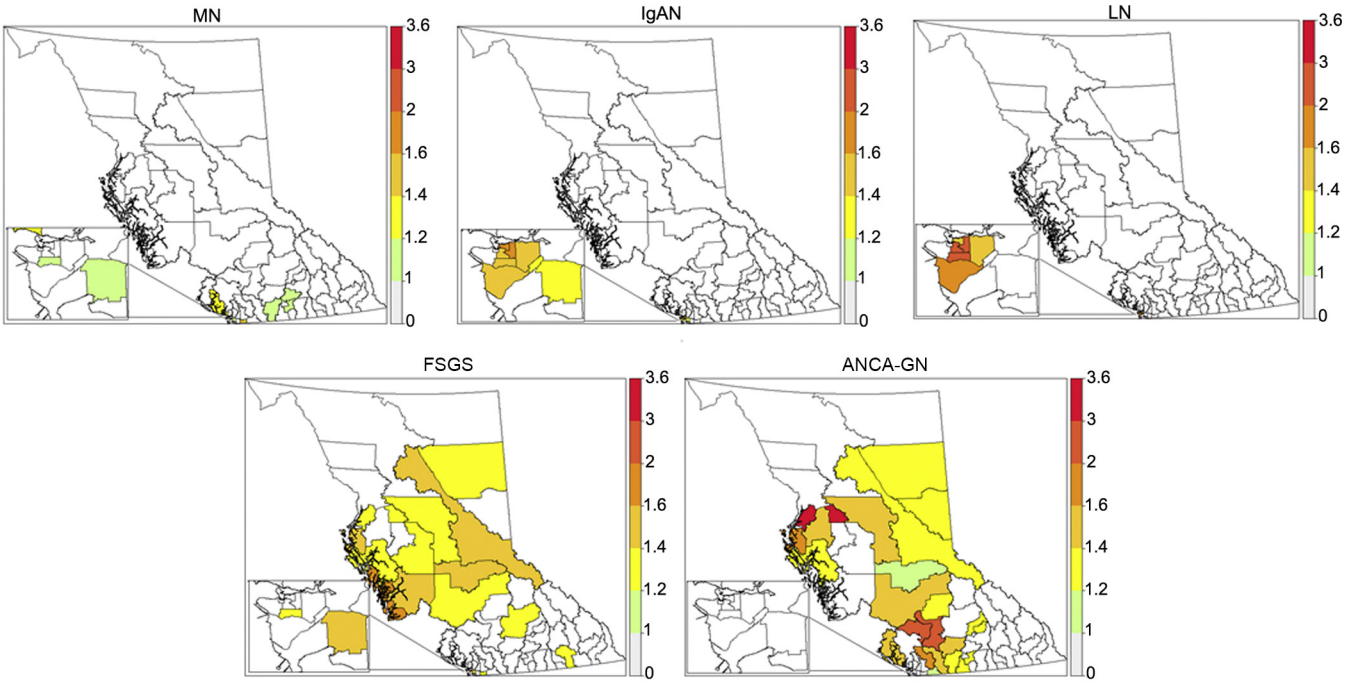

Figure 1 | Location of clusters for membranous nephropathy (MN), IgA nephropathy (IgAN), lupus nephritis (LN), focal segmental glomerulosclerosis (FSGS), and anti-neutrophil cytoplasm antibody–related glomerulonephritis (ANCA-GN). The color-coded magnitude of observed to expected incidence (incidence rate ratio) for each cluster is displayed on the y-axis.

FSGS, both of which had numerous clusters in the central and northern parts of the province.

Geographic clusters and access to nephrology care

Figure 2 illustrates the population density (number of persons per square kilometer [km]) for each region, along with the driving distance (in km) to the nearest nephrology center. Large variability was found in both population density and driving distance among disease-specific clusters (Table 2). The IgAN and LN clusters were located exclusively in urban regions of high population density (range: 1304–6715 persons per km^2) in close proximity to a nephrology center (driving distance range: 3–15 km). In contrast, ANCA-GN, MN, and FSGS clusters were predominantly in rural regions of low population density with potentially large driving distances to the nearest nephrology center. All ANCA-GN clusters were in sparsely populated regions (population density range: 0.4–68 persons per km^2) located a median driving distance of 154 km (range: 10–676 km) from a nephrology center. Similarly, 88% of FSGS clusters were in rural regions with a median driving distance of 386 km (range: 7–950 km) to the nearest nephrology center.

Geographic clustering adjusted for demographic characteristics

In order to examine whether the observed geographic clustering was independent of regional differences in age, sex, and race, we combined the identified clusters into larger "super-regions" that could be included in a multivariable model. For each glomerular disease subtype, contiguous geographic clusters with similar magnitudes of risk were aggregated into super-regions (Figure 3 and Supplementary Figure S1). Four super-regions were identified for MN, 4 for IgAN, 6 for FSGS,

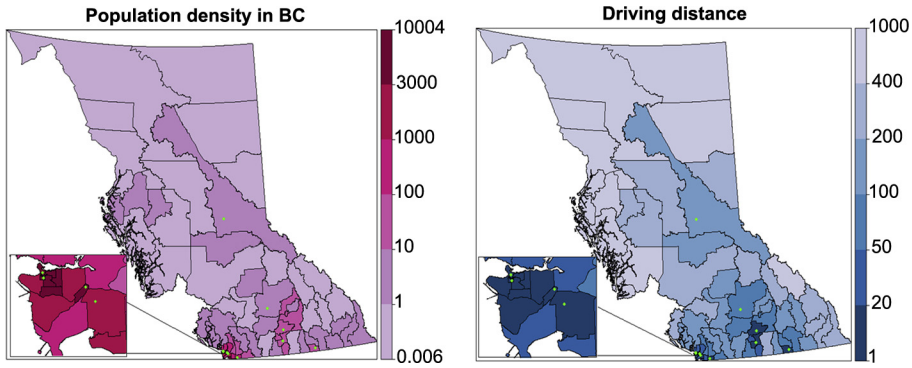

Figure 2 | Population density (number of persons per square kilometer) and driving distance in kilometers to nearest nephrology center (each represented by a green dot) for each region in British Columbia (BC).

Table 2 | Population density (persons per km^2) and driving distance (in km) to nephrology center for each region identified as a cluster, stratified by rural or urban status

Variable	MN	IgAN	FSGS	ANCA-GN	LN
Rural clusters[a]					
N (%) of all clusters	6 (75)	0	15 (88)	25 (100)	0
Population density	45.3 (0.9–334.7)	n/a	0.6 (0.1–334.7)	1.2 (0.4–67.9)	n/a
Driving distance	23 (7–130)	n/a	386 (7–950)	154 (10–676)	n/a
Urban clusters					
N (%) of all clusters	2 (25)	8 (100)	2 (12)	0	6 (100)
Population density	1678.5[b] 4677.2[b]	4240.9 (1304.3–6714.6)	1678.5[b] 4677.2[b]	n/a	5079.7 (1304.3–6714.6)
Driving distance	7[b] 7[b]	7 (3–15)	7[b] 7[b]	n/a	7.5 (3–15)

ANCA-GN, anti-neutrophil cytoplasm antibody–related glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MN, membranous nephropathy.
Values are median (range), unless otherwise indicated.
[a]Rural regions are defined by a population density <400 persons per square kilometer.
[b]Data for each cluster reported rather than median (range).

9 for ANCA-GN, and 1 for LN. This condensed number of geographic clusters using super-regions accounted for the majority (67%–94%) of the interregional variability in disease incidence that was identified at the region level (Supplementary Table S2). Thus, we included these super-regions in disease-specific multivariable models, comparing the fixed effects in a model with super-regions to the fixed effects in a model with super-regions plus the region-level covariates age, sex, and race (Table 3). For MN, IgAN, FSGS, and ANCA-GN, the inclusion of age, sex, and race resulted in minimal changes to the point estimates for the IRR for each super-region. In LN, the geographic variability explained by the super-region was entirely accounted for by region-level demographics, as indicated by the complete attenuation of the super-region IRR in the multivariable model.

DISCUSSION

Using population-level data, a centralized renal biopsy database, and a Bayesian spatial model, we provide the first robust estimates of the geographic variability in the incidence of glomerular diseases. We identified geographic clusters of disease that varied by disease and had observed incidence

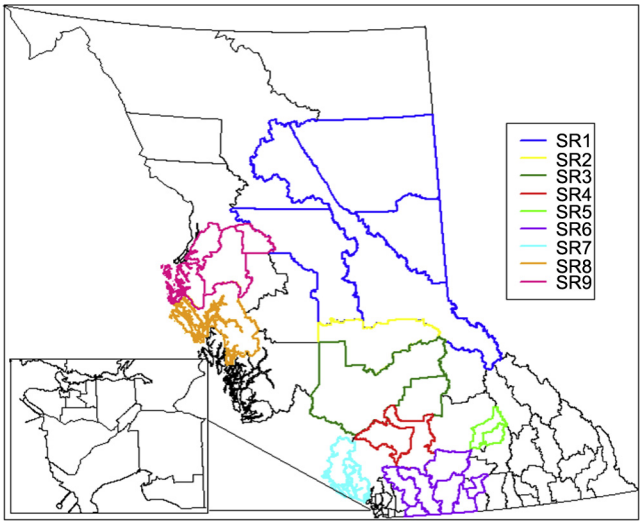

Figure 3 | Location of super-regions (SRs) for anti-neutrophil cytoplasm antibody–related glomerulonephritis.

Table 3 | The incidence rate ratio (95% credible interval) for each super-region before and after adjustment for region-level demographic risk factors (age, sex, and race)

Super-region number	Model with super-regions only	Model with super-regions and demographic covariates[a]
Membranous nephropathy		
1	1.98 (1.07, 3.45)	1.94 (0.96, 3.80)
2	1.14 (0.85, 1.51)	1.14 (0.84, 1.51)
3	1.16 (1.04, 1.30)	1.17 (1.02, 1.35)
4	1.08 (0.96, 1.22)	1.08 (0.94, 1.24)
IgA nephropathy		
1	2.37 (1.49, 3.83)	2.30 (1.27, 4.24)
2	1.83 (1.13, 2.97)	1.77 (1.05, 2.97)
3	2.04 (1.14, 3.68)	1.91 (0.86, 4.27)
4	1.58 (0.96, 2.61)	1.54 (0.92, 2.58)
FSGS		
1	2.80 (1.86, 4.37)	2.96 (1.79, 5.19)
2	1.87 (1.00, 3.42)	1.62 (0.79, 3.30)
3	2.48 (0.83, 6.32)	2.14 (0.68, 5.92)
4	1.33 (0.69, 2.44)	1.26 (0.47, 3.53)
5	1.97 (1.30, 3.01)	1.87 (0.85, 4.51)
6	1.58 (0.87, 2.77)	1.69 (0.63, 4.79)
ANCA -GN		
1	1.98 (1.22, 3.25)	1.99 (1.17, 3.43)
2	1.15 (0.27, 3.58)	1.17 (0.27, 3.74)
3	2.00 (0.88, 4.12)	1.91 (0.81, 4.14)
4	3.07 (1.97, 5.40)	3.15 (1.50, 6.33)
5	1.84 (0.75, 3.99)	1.77 (0.71, 4.01)
6	2.13 (1.37, 3.25)	2.09 (1.32, 3.27)
7	2.07 (0.93, 4.17)	1.95 (0.83, 4.22)
8	1.57 (0.24, 3.23)	1.53 (0.23, 6.30)
9	2.70 (1.28, 5.45)	2.42 (0.93, 6.08)
Lupus nephritis		
1	2.07 (1.38, 3.10)	1.01 (0.88, 1.95)

ANCA-GN, anti-neutrophil cytoplasm antibody–related glomerulonephritis; FSGS, focal segmental glomerulosclerosis.
In each case, the reference group consists of all regions not identified as clusters for that glomerulonephritis subtype.
[a]Adjusted for region-level age, sex, and race.

rates up to 3-fold higher than expected. Apart from LN, the clusters of increased disease incidence were not explained by regional differences in age, sex, and race. For MN, ANCA-GN, and FSGS, disease clusters were located in rural regions of low population density with considerable driving distances to the nearest nephrology center, and therefore represent disadvantaged subpopulations with a combination of high-risk kidney disease and limited access to necessary health care resources.

To date, high-quality research on the incidence of various types of glomerular diseases has been limited. Most prior studies have been based on data from regional biopsy or ESKD registries.[2] The former approach is subject to bias due to the absence of a clearly defined source population and is therefore unable to generate true incidence rates or investigate risk factors such as geography and demographics. Using ESKD registries identifies only those patients who have progressed to end-stage disease, rather than incident cases at the time of onset. A recent study from the United States used a population of insured patients to estimate the incidence of all-cause glomerulonephritis using administrative data.[6] A significant limitation was the inability to describe incidence rates by specific glomerular disease subtypes. The absence of accurate data on the incidence of glomerular diseases is a glaring omission in a field dominated by high-quality basic science and translational research, and it limits the ability to advocate for glomerular disease–specific health care resources[16] and plan recruitment for clinical trials.[17]

To address this deficiency, we leveraged data from a unique provincial, centralized pathology database that records all patients with a biopsy-proven diagnosis of glomerular disease from a large, well defined, and geographically diverse source population. This approach allowed us to accurately define the at-risk population and adjust our analyses for population-level demographics. The relative rarity of individual diseases poses additional analytic challenges in attempts to examine regional variability in incidence. Areas that are less densely populated are expected to have low numbers of cases, and adjacent areas might be expected to have incidence rates that are more similar, compared with areas further away. Conventional frequentist approaches such as Poisson models do not reliably account for these 2 issues—over-dispersion and spatial autocorrelation—resulting in greater uncertainty in estimates. We therefore employed a dedicated Bayesian spatial model that accounts for these sources of error and has been used previously to define incidence patterns in other rare diseases such as multiple sclerosis[18] and anti-glomerular basement membrane disease.[19]

Our results identified geographic clusters with a disproportionately high incidence of glomerular disease that could not have been predicted from regional demographics and that represent subpopulations with a mismatch of high disease incidence and limited availability of health care resources. This mismatch is likely to place a significant travel burden on patients, reduce access to regular laboratory and clinical monitoring, and add limitations to the use of the potent immune therapy often required for management of glomerular disease. Rural disparities in access to complex and resource-intensive health care have been observed in other diseases and are equally likely to apply to glomerular disease. For example, a study of kidney disease patients found that those who resided more than 20 km from a dialysis center were less likely to receive an optimal vascular access for dialysis.[20] In the general population, individuals living in rural regions have been shown to have reduced access to cancer screening programs and specialist-delivered care.[21,22] Those with large driving distances may have more restricted therapeutic options and are likely to wait longer to receive appropriate treatment.[23,24] The culmination of these factors may contribute to worse cancer-related survival rates in rural subpopulations.[25]

Although our results are specific to BC, the existence of region- and disease-specific subpopulations at high risk for glomerular disease but with reduced access to care is likely the case in other geographic areas, and it has significant implications for the appropriate planning and delivery of glomerular disease–related health services. Because regions with a disproportionately high incidence of disease cannot be identified based on population demographics alone, our results suggest the need for mandatory central reporting of incident glomerular diseases so that health systems can accurately define their glomerular disease population and allocate the necessary health care resources.

Although the identification of specific underlying causes for the geographic clustering of different glomerular diseases is beyond the scope of this study, the widespread distribution of disease clusters suggests environmental rather than genetic factors. Previous literature has suggested a role of host–environment interactions in the development of IgAN,[26,27] and ANCA-GN.[28,29] Air pollution has been proposed as a potential contributor to the pathogenesis of multiple autoimmune diseases.[30] In China, the incidence of MN may be related[31] to chronic exposure to high levels of fine particulate matter <2.5 μm. Several studies have demonstrated an association of ANCA-associated vasculitis and lupus with occupational risk factors such as agricultural and livestock farming, and carbon monoxide and silica exposure.[32–35] Consistent with these observations, the rural regions of BC with prominent clusters of glomerular disease have common industries known to generate environmental pollutants, including agriculture, farming, forestry, and mining.[36]

These hypotheses require further study, and our results can inform future research seeking to explore the potential role of such environmental exposures in the pathogenesis of glomerular diseases. In IgAN, ANCA-GN, and LN, a large proportion (59%–89%) of overall variability in disease incidence was attributable to geography. However, only in IgAN and ANCA-GN was this geographic variability not explained by demographic risk factors, and therefore these diseases may be best suited for future studies on environmental triggers of disease onset. Conversely, only 18% of variability in the incidence of both MN and FSGS was due to geography,

suggesting that factors unrelated to regional environmental exposures may be driving the bulk of disease susceptibility in these conditions.

Our study has a number of limitations. We included only biopsy-proven cases of glomerular disease; thus, our incidence rates are underestimated, as not all patients with glomerular disease have a kidney biopsy performed. We adjusted our models for age, sex, and race, but other region-level demographic variables, such as socioeconomic factors, could explain some of our findings. Although we sought to restrict cases of MN, IgAN, and FSGS to those with immune etiology, the potential for misclassification remains. Anti-phospholipase A2 receptor testing was not available during the study period, which might have helped in the diagnostic classification of MN. The diagnosis of FSGS is notoriously problematic in this context. However, these patients had significant proteinuric kidney disease with a high risk of progression to ESKD; therefore, the implications of our findings in terms of health services delivery are nonetheless valid. Future research is required to investigate the importance of geographic variability in the incidence of glomerular disease with respect to long-term outcomes such as progression to ESKD.

These limitations are balanced by several strengths. The sample sizes for individual diseases were relatively large. All biopsies performed during the study period were processed and analyzed in a single tertiary referral center. The source population was heterogeneous with respect to race and ethnicity, and therefore our findings are generalizable to a multiethnic population.

In conclusion, we have revealed the substantial geographic variability in the incidence of individual glomerular diseases, which is largely unexplained by age, sex, and race. Prominent clusters of MN, FSGS, and in particular, ANCA-GN were identified in rural, sparsely populated regions with limited access to nephrology health care resources. Our findings emphasize the need for robust epidemiologic studies in glomerular disease to better understand disease incidence and identify disadvantaged subpopulations for whom targeted interventions are required to ensure the availability of specialized care and optimal treatment.

METHODS

Design, setting and participants

This retrospective, population-level cohort study included all individuals with glomerular disease diagnosed from a native kidney biopsy between 1 January 2000 and 31 December 2012 in BC, a Canadian province with a universal health care system. All renal biopsy specimens in mainland BC are processed in a single tertiary referral laboratory, are registered in the BC Renal Pathology Database, and are analyzed by a dedicated renal histopathologist who records the primary diagnosis using a standardized coding system. We included the glomerular diseases membranous nephropathy, IgA nephropathy, and FSGS. We were most interested in cases with a higher likelihood of immune etiology. We therefore excluded cases that, based on histologic features and the clinical data provided at the time of biopsy, were deemed by the pathologist to be likely to be due to other causes, such as infection, medications, systemic autoimmune disease, hypertension, and diabetes. We also included patients with lupus nephritis and ANCA-associated vasculitis with glomerular involvement on biopsy. Cases with a previous biopsy showing the same glomerular disease, and cases with missing data for patient location, were excluded (Supplementary Figure S2). This sample is therefore a population-level cohort of all incident cases of these glomerular disease subtypes in mainland BC from 2000 to 2012. Approval for this study was granted by the research ethics board of the University of British Columbia.

Data sources

Patient-level data. The BC Renal Pathology Database contains biopsy details, clinical data at the time of biopsy, and a unique patient identifier.[16] The pathology database was linked to the following provincial health administrative databases using the unique patient identifier: (i) the BC Renal Agency, to capture race, additional laboratory and blood pressure data, and ESKD status; (ii) BC Vital Statistics, to capture date of birth and sex; (iii) the BC Ministry of Health Medical Services Plan, to capture location of residence. Further information about each data source can be found in the Supplementary Methods. We divided BC into 74 unique, nonoverlapping geographic units (hereafter referred to as "regions") using existing boundaries for local health authorities. We assigned each patient to a specific region based on their location of residence in the year of their biopsy.

Population-level data. Region-level annual population and distributions of age, sex, and race were provided by BC Stats (www.bcstats.gov.bc.ca). Race was taken from the Canadian census and allocated based on the closest census year (2001, 2006, or 2011). We combined annual estimates for region-level data from the years 2000 to 2012 using a weighted mean based on the relative yearly population to the total person-years of follow-up in each region. A region was defined as urban or rural based on having a population density greater than or less than 400 persons per km^2, respectively (Statistics Canada: www.statcan.gc.ca). Distance to a nephrology center was calculated as the driving distance in km from the centroid of each region to the nearest hospital that had a dedicated nephrology service.

Statistical analysis

To examine regional differences in the incidence of GN, we employed a hierarchical Bayesian spatial model commonly used to study geographic variability in incidence rates.[37] This methodology has been applied across numerous health arenas, including heart disease, infections, and public health interventions.[38–41] A Bayesian approach is preferred in this setting for several reasons. First, an incidence rate (or incidence rate ratio) can be estimated for each region (the unit of analysis). Second, the incorporation of 2 random effects accounts for both autocorrelation among adjacent regions (spatial random effect) and over-dispersion arising from potentially large variation across smaller, less-populated regions (random error). These components of variance, the spatial effect and random error, are estimated by borrowing information from all units of analysis. Third, this particular model allows for the inclusion of region-level covariates.[18] The model assumes that the logarithm of the incidence rate in each region depends on the spatial effect, the random error, and where applicable, the region-level covariates age, sex, and race. This approach accounts for the assumption that regions closer together are expected to have incidence rates that are more similar to one another than do regions further apart, by applying a weight to

the spatial random effect for regions that are adjacent to one another. A detailed description of the model is provided in the Supplementary Methods.

Bayesian models were fit separately for each glomerular disease subtype. From the fitted model, we computed the IRR for each region, defined as the incidence rate in a particular region divided by the overall incidence rate in BC. Regions with an IRR >1 have a higher than expected incidence, and regions with an IRR <1 have a lower than expected incidence. For each disease, the amount of variability in incidence explained by geographic differences was taken as the proportion of overall variability accounted for by the spatial random effect in the null model with no covariates (calculated as the SD of the spatial random effect divided by the sum of the SDs of both the spatial random effect and the random error term).[42]

The Bayesian model was adjusted for the ecological (region-level) covariates age, sex, and race because these are common demographic factors known to be associated with the incidence of glomerular disease.[43–48] We identified the best functional form for each region-level covariate using univariable models (see Supplementary Methods). When necessary, continuous covariates were categorized using Jenks' natural breaks.[49] The multivariable models with age, sex, and race were used to generate region-specific IRRs for each disease to identify potential clusters. The parameters in the model were estimated from Markov chain Monte Carlo simulation with prior probability distributions (see Supplementary Methods).[50] A region was identified as a potential cluster when >80% of simulations estimated an IRR >1 for that region.[37] Finally, we aggregated contiguous regions that were identified as clusters into larger "super-regions." The amount of variability in incidence explained by the super-regions was taken as the percent change in the SD of the spatial random effect, comparing the null model with no covariates to a model including the super-region variable. The super-regions were then included in a multivariable model along with demographic covariates in order to estimate the IRR for each super-region independent of regional differences in age, sex, and race. The reference group for the super-region variable consisted of all other regions not identified as clusters in the preceding analysis.

DISCLOSURE

All the authors declared no competing interests. All inferences, opinions, and conclusions drawn in this article are those of the authors, and do not reflect the opinions or policies of the data steward(s).

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SUPPLEMENTARY MATERIAL

Table S1. Demographics of mainland British Columbia. Age, sex, and race data were taken from the 2006 Canadian Census.

Table S2. The unexplained variability in each model attributed to geographic variability (spatial random effect) and heterogeneity (random error). The base model includes no covariates and describes the overall state of geographic variation in the incidence of each glomerular disease. The spatial effect from the model with super-regions is compared to that from the base model, to describe the amount of overall geographic variation explained by the super-regions (% change in the spatial effect). Alpha is the percentage of total unexplained variability in each model (i.e., not accounted for by covariates) that is due to geographic variability. It is calculated by dividing the spatial random effect by the sum of the spatial random effect and random error. Both random effects (spatial effect and random error) are expressed in terms of their SD.

Table S3. Best-fitting univariate associations, between region-level demographic variables and the incidence of each glomerular disease, that were used in the multivariable hierarchical Bayesian models to identify geographic clusters of disease.

Figure S1. Location of super-regions (SRs) for membranous nephropathy (MN), IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), and lupus nephritis (LN).

Figure S2. Flowchart of case ascertainment. FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MN, membranous nephropathy.

Supplementary Methods. Description of data sources and Bayesian spatial model.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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