Article

Temporal and Demographic Trends in Glomerular Disease Epidemiology in the Southeastern United States, 1986–2015

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Abstract

Background and objectives Large-scale, contemporary studies exploring glomerular disease epidemiology in the United States are lacking. We aimed to determine 30-year temporal and demographic trends in renal biopsy glomerular disease diagnosis frequencies in the southeastern United States.

Design, setting, participants, & measurements In this cross-sectional, observational study, we identified all patients with a native kidney biopsy specimen showing one of 18 widely recognized glomerular disease diagnoses referred to the University of North Carolina Chapel Hill Division of Nephropathology between 1986 and 2015. Biopsy era (1986–1995, 1996–2005, and 2006–2015) and demographics (age, sex, and race) were our primary and secondary predictors, respectively, and the relative frequency of each glomerular disease diagnosis was our primary outcome.

Results Among 21,374 patients (mean age =48.3±18.3 years old; 50.8% men; 56.8% white; 38.3% black; 2.8% Latino; 1.4% Asian; 0.8% other), the frequency of diabetic glomerulosclerosis in renal biopsy specimens increased dramatically over the three decades (5.5%, 11.4%, and 19.1% of diagnoses, respectively; P for trend <0.001). The frequency of FSGS initially increased but then declined (22.6%, 27.2%, and 24.7%, respectively; P for trend =0.64). The frequencies of other common glomerular disease subtypes remained stable (IgA nephropathy and ANCA/pauci-immune GN) or declined (minimal change disease, membranous nephropathy, membranoproliferative GN, and lupus nephritis). These temporal trends were largely preserved within all demographic subgroups, although cross-sectional frequency distributions differed according to age, sex, and race.

Conclusions We identified significant changes in relative renal biopsy frequencies of many glomerular disease subtypes over three decades. Temporal trends were consistently observed within all major demographic groups, although relative predominance of individual glomerular disease subtypes differed according to patient age, sex, and race. We propose that exploration of behavioral and environmental exposures that likely underlie these findings should be the focus of future hypothesis-driven research.

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Introduction

Epidemiologic studies reveal important insights into factors associated with glomerular disease development or progression and inform predictions of the relative likelihood of individual glomerular disease diagnoses for a given patient. The disproportionally high risks for FSGS in blacks and IgA nephropathy in Asians encouraged the discovery of racially determined genetic risk variants (1,2). Associations between population sanitation standards or socioeconomic status and risks for certain GN subtypes suggest an etiologic role for environmental and lifestyle factors in disease pathogenesis (3,4). Thus, identifying temporal changes in glomerular disease epidemiology within a geographic region might reliably inform future hypothesis-driven studies and public health interventions.

Within the United States, prior studies exploring glomerular disease epidemiology identified a marked increase in the frequency of FSGS at the end of the 20th century (5–9). Whether this trend continued into the 21st century has not been established, although a small study (n=204) from Chicago suggested that the frequency of FSGS (2000–2011) might now be lower than that of membranous nephropathy among blacks (10). Temporal trends are less consistent across studies for other glomerular disease subtypes, explained by differences in population demographics (*e.g.*, white [9], military [11], or urban-dwelling patients [7]) or clinical inclusion criteria (*e.g.*, nephrotic syndrome [7,8] versus any glomerular disease [9,12]). Frequencies of especially rare glomerular diseases are seldom reported.

The Division of Nephropathology at the University of North Carolina (UNC) at Chapel Hill has provided a nephropathology service to the UNC and academic and community practices throughout the southeastern

United States since the 1970s. By examining native kidney biopsy cases from patients submitted between 1986 and 2015, we aimed to describe temporal trends in glomerular disease frequencies over three decades and explore the influence of demographic factors on glomerular disease frequency distributions.

Materials and Methods

Patient Population

All native kidney biopsy specimens referred to the Division of Nephropathology at the UNC (1986–2015) with one of 18 widely recognized diagnostic categories of glomerular disease were considered for study inclusion. The referral population was derived predominantly from residents of North Carolina and its neighboring states, including Virginia, West Virginia, Tennessee, South Carolina, and Georgia. If a patient had multiple biopsies with a glomerular disease diagnosis, only the first was retained for this study. If more than one glomerular disease diagnosis was made from a single biopsy specimen, that which seemed to be the major cause for the renal dysfunction prompting the biopsy was chosen as the study diagnosis (*i.e.*, if the primary diagnosis was a glomerular disease, then we retained this diagnosis; otherwise, we searched for the presence of a glomerular disease as a secondary diagnosis, such that a single predominant glomerular disease was elucidated for each patient).

Data Source

All renal biopsy specimens were processed by standard light, immunofluorescence, and electron microscopy procedures. Diagnoses were those made by experienced nephropathologists involved in the clinical care of patients. For analysis, all Columbia variants of FSGS (13), all Ehrenreich and Churg stages of membranous nephropathy (14), and all International Society of Nephrology/Renal Pathology Society classes of lupus nephritis (15) were grouped into respective FSGS, membranous nephropathy, and lupus nephritis categories. Dense deposit disease (membranoproliferative GN [MPGN] type 2) was analyzed separately from other forms of MPGN. Immune complex MPGN and C3 GN with an MPGN pattern of injury (including so-called types 1 and 3 MPGN) were included in the MPGN category, because the distinction between these two disease entities was only recently recognized (16). The uncommon C1q and IgM mesangial nephropathies were subsumed in minimal change disease and FSGS categories on the basis of the light microscopic pattern of injury. A diagnosis of pauci-immune necrotizing and crescentic GN was on the basis of pathologic phenotype without requiring serologic ANCA positivity. Antiglomerular basement membrane GN that was also ANCA positive was included in the antiglomerular basement membrane GN category.

Demographic data were abstracted from biopsy referral forms completed by referring nephrologists or available medical records.

Exposures, Outcomes, and Covariates

Temporal era was our primary exposure, categorized in to three consecutive 10-year time intervals (1986–1995, 1996–2005, and 2006–2015) for tabular presentation and data analysis and six consecutive 5-year time intervals (1986–1990, 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015) for plotting. Glomerular disease subtype frequency was our primary outcome. As secondary outcomes, we also examined temporal trends in glomerular disease frequencies within demographic subgroups as well as by typical mode of clinical presentation for a given subtype (nephrotic versus nephritic syndrome [17]). To explore combined influences of age, sex, and race, we evaluated glomerular disease frequency distributions across age categories stratified by patient sex and race.

Statistical Analyses

Categorical variables were expressed as frequencies (percentages) and compared using chi-squared or Fisher exact testing as appropriate. When analyzing differences across study eras, P for trend values are reported. Continuous variables were expressed as means (SDs) or medians (interquartile ranges) and compared using ANOVA or Kruskall–Wallis testing as appropriate. Statistical analyses were performed using SAS Enterprise Guide, version 6.1 (SAS, Cary, NC). A two-sided P value of <0.05 was considered statistically significant when analyzing demographic data, and a Bonferroni correction for multiple comparisons (0.05/18=0.0027) was applied when analyzing trends across 18 glomerular disease subtypes.

Institutional review board (IRB) approval for the study was obtained from the UNC Biomedical IRB (Study 97–0523).

Results

Patient Population

In total, 38,472 kidney biopsies (33,391 native and 5081 transplant) were evaluated between 1986 and 2015. Biopsy frequencies increased annually from 390 (1986) to 1923 (2015). Of these, 22,516 native kidney specimens had one of the 18 study diagnoses. From these, 1142 repeat biopsies in 1016 patients were excluded, leaving a final study population of 21,374 patients with one of the 18 glomerular disease subtypes of interest diagnosed on an initial native kidney biopsy.

Average patient age was 48.3 ($\pm$18.3) years old, 50.8% were men, 56.8% were white, and 38.3% were black (Table 1). With each consecutive decade, patients were older at the time of biopsy (mean age =45.1$\pm$19.1, 46.9$\pm$18.2, and 50.4$\pm$17.9 years old, respectively; $P<0.001$). The largest number of specimens (54.4% of all samples with a documented state of origin) was received from centers in North Carolina, whereas most of the remaining specimens (42.5%) came from other southeastern states, including Georgia, South Carolina, Tennessee, and Virginia (Supplemental Table 1). The demographics of our study cohort were compared with those of the population of North Carolina. Percentage of men in our cohort was similar to that reported for North Carolina in the 2010 Census (51% men) (18) and did not change significantly over time. Black race was more prevalent in our cohort (38%) than at the state level (22%), whereas white race (57% versus 69%, respectively), Latino ethnicity (3% versus 8%, respectively), and Asian race (1% versus 2%, respectively) were less prevalent. In both populations, Asian race and Latino ethnicity increased over time, whereas white race declined, and black race remained stable.

Table 1. Temporal trends in patient demographics among the study cohort of patients with specified glomerular disease diagnoses

Demographic Characteristics	1986–1995, *n*=3257	1996–2005, *n*=7954	2006–2015, *n*=10,163	Total, *n*=21,374	*P* Value
Age, mean (SD)	45.1 (19.1)	46.9 (18.2)	50.4 (17.9)	48.3 (18.3)	<0.001
Age category, yr, % (*n*)					<0.001
0–17	8.3 (265)	5.3 (417)	3.3 (334)	4.8 (1016)	
18–39	32.0 (1020)	30.6 (2415)	24.8 (2518)	28.0 (5953)	
40–64	40.2 (1282)	44.5 (3515)	47.0 (4772)	45.1 (9569)	
>64	19.6 (624)	19.6 (1547)	24.9 (2525)	22.1 (4696)	
Missing age, %	2.0	0.8	0.1	0.7	
Men, % (*n*)	51.9 (1689)	50.1 (3949)	51.1 (5185)	50.8 (10,823)	0.17
Missing sex, %	0.1	0.8	0.1	0.3	
Race, % (*n*)					<0.001
White	64.1 (1610)	56.6 (3782)	54.7 (4714)	56.8 (10,106)	
Black	34.5 (867)	39.9 (2662)	38.2 (3292)	38.3 (6821)	
Latino	0.6 (14)	1.8 (123)	4.2 (360)	2.8 (497)	
Asian	0.0 (1)	1.0 (69)	2.0 (170)	1.4 (240)	
Other	0.8 (19)	0.6 (42)	0.9 (81)	0.8 (142)	
Missing race %	22.9	16.0	15.2	16.7	

Percentages (except missing percentages) represent column percentages among patients with complete data.

Temporal Trends in Glomerular Disease Frequency

Renal biopsy frequencies by study era and glomerular disease subtype are provided in Figure 1 and Table 2. In the earliest era (1986–1995), FSGS predominated (22.6% of studied patients) followed by membranous nephropathy (17.8%). In the middle (1996–2005) and later (2006–2015) eras, FSGS still predominated (27.2% and 24.7%, respectively) but was followed by lupus nephritis (13.9%) and

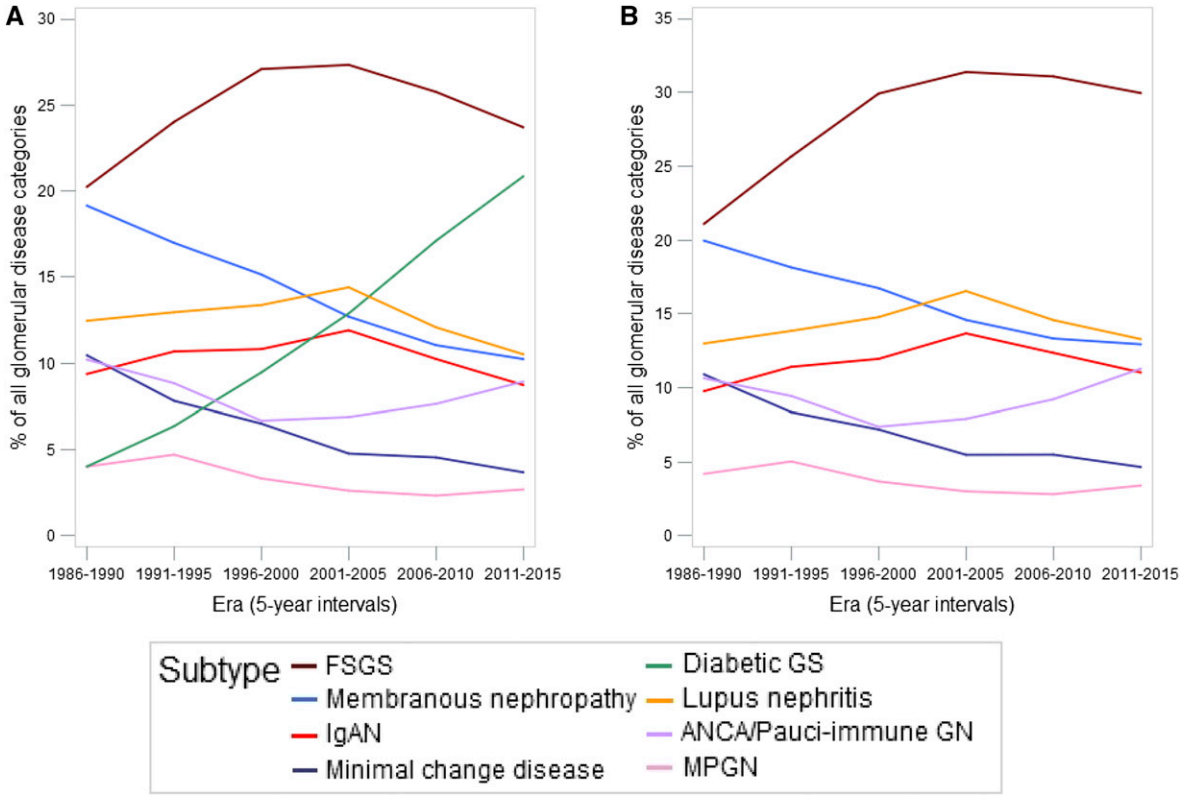

Figure 1. | Temporal trends in the relative renal biopsy frequencies of the most common glomerular disease subtypes, 1986–2015. (A) Frequencies of the eight most common glomerular disease subtypes shown as a proportion of the entire cohort. (B) Frequencies of the seven most common glomerular disease subtypes shown as a proportion of remaining subtypes after excluding diabetic glomerulosclerosis (GS). IgAN, IgA nephropathy; MPGN, membranoproliferative GN excluding dense deposit disease.

membranous nephropathy (13.8%) in the middle era and diabetic glomerulosclerosis (19.1%) in the most recent era.

Significant temporal changes in glomerular disease subtype relative frequencies were observed (Figure 1, Table 2). Most notable was a steady increase in the frequency of diabetic glomerulosclerosis over the three study decades (5.5%, 11.4%, and 19.1% of diagnoses, respectively; P for trend <0.001). The frequency of FSGS increased initially, but then, it plateaued and ultimately declined (22.6%, 27.2%, and 24.7%, respectively; P=0.64). The frequencies of membranous nephropathy (17.8%, 13.8%, and 10.6%, respectively; P<0.001) and minimal change disease (8.8%, 5.5%, and 4.1%, respectively; P<0.001) declined substantially over the study interval, whereas those of lupus nephritis (12.8%, 13.9%, and 11.2%, respectively; P<0.001) and MPGN types 1 or 3 (4.5%, 2.9%, and 2.5%, respectively; P<0.001) declined more modestly. The frequencies of IgA nephropathy (10.2%, 11.4%, and 9.4%; P=0.004) and ANCA/pauci-immune GN (9.3%, 6.8%, and 8.3%; P=0.14) remained stable. As a sensitivity analysis, we re-examined the frequencies of remaining subtypes after excluding diabetic glomerulosclerosis to ensure that large shifts in the frequency of this diagnosis did not unduly influence frequency distributions among the remaining 17 subtypes. Findings were not materially different (Figure 1B).

Among more rare subtypes (biopsy frequency <3%), some significant temporal trends were also observed (Table 2). Significant increases were observed in thin basement membrane lesion and monoclonal Ig deposition disease frequencies.

Temporal Trends in Glomerular Disease Frequencies by Age, Sex, and Race

Temporal trends in men or women mirrored those in the overall cohort (Supplemental Figure 1). However, differences between sexes were observed at a cross-sectional level. For example, lupus nephritis was more frequent in women than men (20.5% versus 4.7%, respectively), whereas the opposite was true for IgA nephropathy (7.7% versus 12.8%, respectively). Sex distributions by glomerular disease subtype are shown in Supplemental Figure 2 and Table 3.

For black or white patients, temporal trends were also similar to those observed in the full cohort (Supplemental Figure 1). Comparing races cross-sectionally, however, lupus nephritis (20.9% versus 6.3%, respectively) and FSGS (33.6% versus 20.4%, respectively) were more frequent and IgAN (2.3% versus 14.9%, respectively) and ANCA/pauci-immune GN (3.3% versus 11.4%, respectively) less frequent among blacks. Racial distributions, by subtype, are presented in Supplemental Figure 2 and Table 3.

Table 2. Temporal trends in the renal biopsy frequencies of glomerular disease subtypes among the study cohort of patients with specified glomerular disease diagnoses

Glomerular disease subtype	1986–1995, n=3257	1996–2005, n=7954	2006–2015, n=10,163	Total, n=21,374
Nephrotic subtypes				
FSGS	22.6 (737)	27.2 (2165)	24.7 (2506)	25.3 (5408)
Diabetic glomerulosclerosis[a]	5.5 (179)	11.4 (903)	19.1 (1942)	14.2 (3024)
Membranous nephropathy[a]	17.8 (579)	13.8 (1097)	10.6 (1078)	12.9 (2754)
Minimal change disease[a]	8.8 (286)	5.5 (441)	4.1 (415)	5.3 (1142)
MPGN[a]	4.5 (145)	2.9 (233)	2.5 (256)	3.0 (634)
Amyloidosis	2.2 (73)	2.0 (158)	2.5 (252)	2.3 (483)
MIDD[a]	0.6 (20)	0.6 (51)	1.6 (160)	1.1 (231)
Dense deposit disease	0.3 (8)	0.1 (9)	0.2 (22)	0.2 (39)
Fabry disease[b]	0.1 (3)	0.1 (11)	0.0 (2)	0.1 (16)
Collagenofibrotic glomerulopathy	0.1 (2)	0.0 (2)	0.0 (1)	0.0 (5)
Total	62.4 (2032)	63.7 (5070)	65.3 (6634)	64.3 (13,736)
Nephritic subtypes				
Lupus nephritis[a]	12.8 (416)	13.9 (1109)	11.2 (1142)	12.5 (2667)
IgAN[c]	10.2 (332)	11.4 (908)	9.4 (958)	10.3 (2198)
ANCA/pauci-immune GN	9.3 (304)	6.8 (540)	8.3 (846)	7.9 (1690)
TBM lesion[a]	1.9 (63)	1.3 (101)	3.0 (304)	2.2 (468)
Fibrillary GN	1.5 (48)	1.2 (99)	1.4 (141)	1.4 (288)
Anti-GBM nephritis[c]	1.1 (37)	1.0 (82)	0.8 (77)	0.9 (196)
Alport syndrome	0.6 (20)	0.4 (35)	0.5 (50)	0.5 (105)
Immunotactoid GN	0.2 (5)	0.1 (10)	0.1 (11)	0.1 (26)
Total	37.6 (1225)	36.3 (2884)	34.7 (3529)	35.7 (7638)

All values represent column percentages (n). MPGN, membranoproliferative GN (nondense deposit disease); MIDD, monoclonal immune deposition disease; IgAN, IgA nephropathy; TBM, thin basement membrane; GBM, glomerular basement membrane.
[a]Chi-squared test for trend, P<0.003.
[b]Fisher exact test, P<0.05 but P>0.003.
[c]Chi-squared test for trend, P<0.05 but P>0.003.

Table 3. Demographic characteristics (sex, race, and age) of patients with each of the 18 studied glomerular disease subtypes

Glomerular disease subtype	Men, % (*n*)	Race, % (*n*)					Mean Age (SD), yr
		White	Black	Latino	Asian	Other	
Nephrotic subtypes							
FSGS	57.1 (3078/5388)	50.6 (2293/4535)	45.4 (2060/4535)	2.6 (117/4535)	0.9 (39/4535)	0.6 (26/4535)	47.4 (18.0)
Diabetic glomerulosclerosis	54.1 (1632/3019)	51.5 (1327/2575)	44.6 (1148/2575)	2.7 (70/2575)	0.7 (18/2575)	0.4 (11/2575)	56.2 (13.0)
Membranous nephropathy	57.6 (1580/2745)	60.2 (1368/2272)	36.1 (821/2272)	2.2 (49/2272)	0.9 (20/2272)	0.6 (14/2272)	51.2 (16.2)
Minimal change disease	52.4 (595/1136)	61.1 (560/916)	33.0 (302/916)	2.3 (21/916)	2.1 (19/916)	1.5 (14/916)	43.7 (22.4)
MPGN	54.8 (344/628)	71.5 (358/501)	23.0 (115/501)	3.8 (19/501)	[a]	[a]	50.8 (19.3)
Amyloidosis	55.0 (264/480)	70.3 (286/407)	27.3 (111/407)	[a]	[a]	[a]	62.9 (11.1)
MIDD	58.7 (135/230)	66.3 (134/202)	30.7 (62/202)	[a]	[a]	[a]	61.8 (12.5)
Dense deposit disease	41.0 (16/39)	70.0 (21/30)	[a]	[a]	[a]	[a]	33.1 (20.1)
Fabry disease	87.5 (14/16)	84.6 (11/13)	[a]	[a]	[a]	[a]	40.8 (14.6)
Collagenofibrotic glomerulopathy	[a]	[a]	[a]	[a]	[a]	[a]	35.6 (31.8)
Nephritic subtypes							
Lupus nephritis	19.2 (509/2656)	28.9 (640/2214)	64.3 (1424/2214)	4.0 (88/2214)	2.1 (46/2214)	0.7 (16/2214)	35.7 (14.3)
IgAN	63.1 (1383/2191)	81.5 (1504/1846)	8.5 (157/1846)	4.1 (76/1846)	3.9 (72/1846)	2.0 (37/1846)	40.7 (17.4)
ANCA/pauci-immune GN	51.7 (872/1686)	81.2 (1151/1417)	15.7 (223/1417)	1.6 (23/1417)	0.9 (12/1417)	[a]	60.6 (16.8)
TBM lesion	24.2 (113/467)	73.3 (274/374)	21.4 (80/374)	4.0 (15/374)	[a]	[a]	39.9 (16.1)
Fibrillary GN	39.6 (114/288)	82.6 (199/241)	17.0 (41/241)	[a]	[a]	[a]	57.0 (11.2)
Anti-GBM nephritis	51.5 (101/196)	85.1 (137/161)	11.2 (18/161)	[a]	[a]	[a]	53.5 (19.3)
Alport syndrome	57.1 (60/105)	76.8 (63/82)	15.9 (13/82)	[a]	[a]	[a]	25.6 (13.7)
Immunotactoid GN	46.2 (12/26)	61.1 (11/18)	[a]	[a]	[a]	[a]	49.7 (16.4)

Denominator is number of persons with nonmissing data for the variable. MPGN, membranoproliferative GN (nondense deposit disease); MIDD, monoclonal immune deposition disease; IgAN, IgA nephropathy; TBM, thin basement membrane; GBM, glomerular basement membrane.

[a]Cell contains <10 patients.

Temporal trends by age category (children, young adults, middle-aged adults, and older adults) are also presented in Supplemental Figure 1. Again, no marked deviations from overall trends were observed, with the exception of a low frequency of diabetic glomerulosclerosis in children. However, cross-sectional differences were again apparent; lupus nephritis was almost as common as FSGS in young adults (25.7% versus 27.3%, respectively) but rare in older adults (2.2%), whereas ANCA/pauci-immune GN was especially frequent in older adults (17.9%) but rare in children (3.9%) and young adults (2.7%). Average ages by glomerular disease subtype are shown in Table 3.

Differences in Glomerular Disease Frequencies by Age Category, Sex, and Race

To further explore the variations in disease frequencies observed between age groups, we examined changes in glomerular disease frequencies across the age spectrum (Figures 2 and 3). Very young (0–9 years old) patients were most likely to have minimal change disease, very old (>79 years old) patients were most likely to have ANCA/pauci-immune GN, and younger or middle-aged adults were most likely to have FSGS. Stratifying by sex and race revealed additional insights; for example, IgAN was most frequent in young adult white men, whereas lupus nephritis peaked in young adult black women.

When glomerular disease subtype frequencies were evaluated as a proportion of all glomerular disease diagnoses in a given age group, the predominance of certain subtypes within particular age groups became even more apparent (Figure 4). Among patients typically presenting with nephrotic syndrome, the likelihood of a renal biopsy diagnosis of minimal change disease declined precipitously after early childhood, whereas diabetic glomerulosclerosis was less likely to be diagnosed in older patients, and FSGS was frequent throughout. Among patients typically presenting with nephritic features, the likelihood of IgA nephropathy declined with advancing age, lupus nephritis peaked in young adulthood, and ANCA/pauci-immune GN was strikingly common in older adults.

Discussion

In this study of 21,374 patients with a biopsy-confirmed glomerular disease diagnosis residing predominantly in the southeastern United States, we identified significant temporal shifts in the epidemiology of many glomerular disease subtypes over the past three decades (1986–2105). Most striking was a marked increase in renal biopsy frequency of diabetic glomerulosclerosis from 5.5% of patients in the earliest decade to 19.1% of patients most recently. This finding was consistently observed within all studied age, sex, and racial groups, with the exception of children. Contemporaneously, we observed an initial increase in frequency of FSGS at the end of the 20th century, as previously reported in other United States cohorts (5–9), followed by a plateau and decline in its frequency more recently, a finding not previously described. At the same time, we observed significant declines in relative frequencies of some other glomerular disease subtypes (*e.g.*, membranous nephropathy, minimal change disease, membranoproliferative GN [excluding dense deposit disease], and lupus nephritis) along with stable frequencies of others (*e.g.*, IgA nephropathy and ANCA/pauci-immune GN). These temporal trends were not explained by large shifts in the demographic composition of our study population and were consistently observed in most age, sex, and racial subgroups.

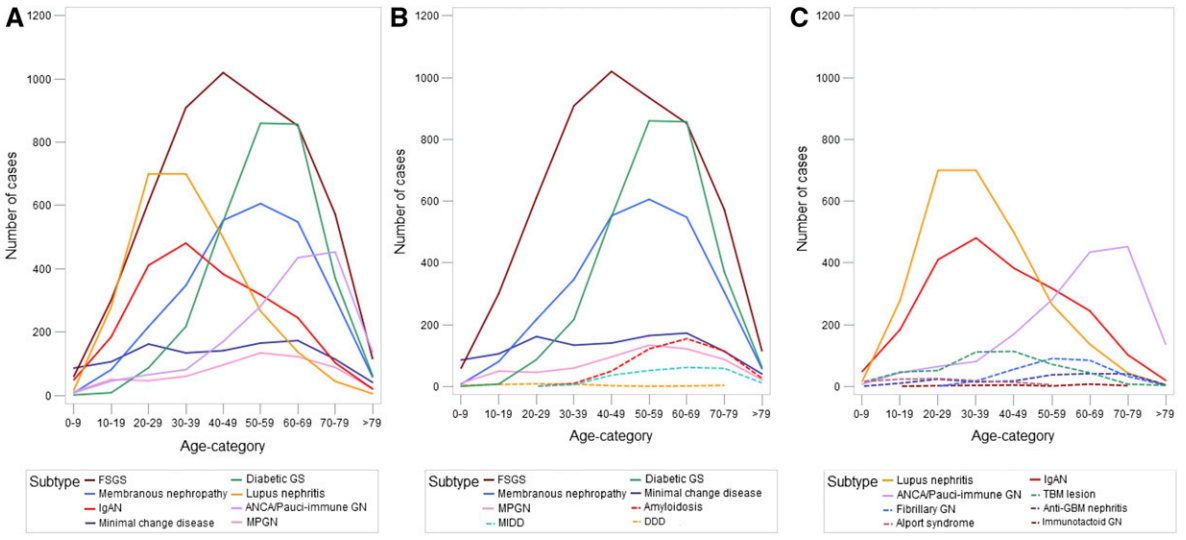

Figure 2. | **Absolute renal biopsy diagnosis frequencies of the most common glomerular disease subtypes according to patient age category.** (A) All subtypes: number of patients with each of the eight most common glomerular disease subtypes shown. (B) Nephrotic subtypes: number of patients with each of the eight most common glomerular disease subtypes that often present with nephrotic syndrome shown (Fabry disease and collagenofibrotic glomerulopathy not shown). (C) Nephritic subtypes: number of patients with each of the eight glomerular disease subtypes that often present clinically with nephritic features shown. DDD, dense deposit disease; GBM, glomerular basement membrane; GS, glomerulosclerosis; IgAN, IgA nephropathy; MIDD, monoclonal immune deposition disease; MPGN, membranoproliferative GN; TBM, thin basement membrane.

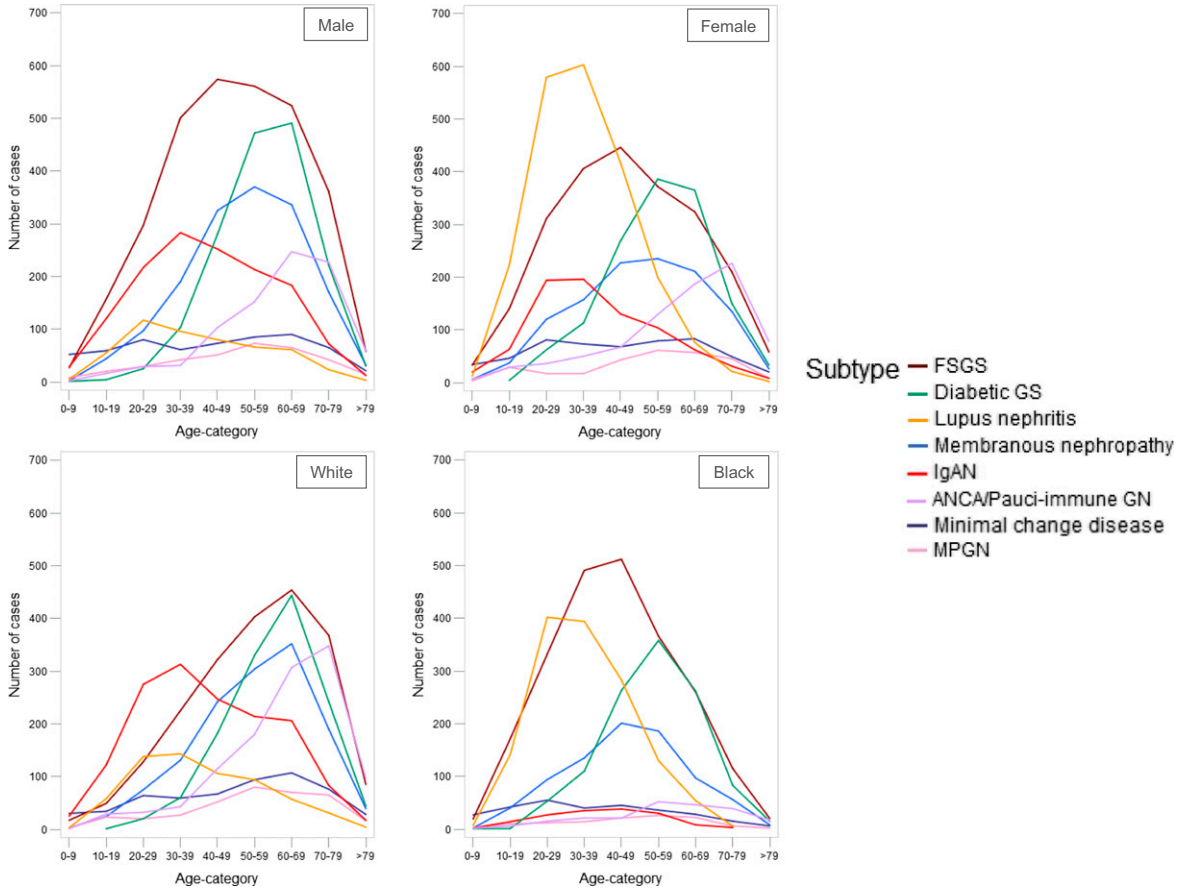

Figure 3. | Absolute renal biopsy diagnosis frequencies of the most common glomerular disease subtypes according to patient age category stratified by sex and race. GS, glomerulosclerosis; IgAN, IgA nephropathy; MPGN, membranoproliferative GN.

Interpretation of our study is complicated by the steadily increasing biopsy referral rate to the UNC over the study interval. Although we report trends in relative disease frequencies (*i.e.*, as a proportion of all biopsies with a glomerular disease diagnosis), we note that, in some cases, a decline in relative disease frequency was accompanied by an increase in absolute disease frequency. The underlying reasons for the rising background biopsy rate may include (*1*) a declining threshold to biopsy patients; (*2*) an increase in the referral population size, mirroring that occurring in North Carolina (19,20); (*3*) increasing numbers of nephrologists referring biopsies to the UNC; or (*4*) true increases in disease incidence. This latter possibility is supported by the fact that diseases with a stronger environmental/lifestyle component to their pathogenesis (*e.g.*, FSGS and diabetic glomerulosclerosis) underwent more marked increases in disease frequency than those with a more clearly established genetic or autoimmune pathogenesis (*e.g.*, ANCA/pauci-immune GN or IgA nephropathy). It is notable that, for some glomerular disease subtypes (*e.g.*, membranous nephropathy or minimal change disease), the absolute numbers of patients declined in the final decade, supporting a true decline in disease incidence. Conversely, the rising frequency of diabetic glomerulosclerosis markedly exceeded the increasing background biopsy referral rate, supporting a true increase in the incidence of this biopsy diagnosis and echoing findings from the general population that the incidence of diabetes mellitus has increased almost twofold between 1995 and 2010 (21).

In an effort to disentangle the influence of shifts in population demographics from that of changes in environmental, lifestyle, or practice pattern factors, we evaluated for temporal changes in the sex, age, or racial composition of our study cohort in addition to examining temporal trends in glomerular disease frequencies within several demographic subgroups. In summary, we did not identify convincing evidence that demographic shifts in our study population were responsible for the changes in glomerular disease frequencies that we observed and suggest that changes in lifestyle/environmental factors or clinical practice are more likely to underlie our findings.

Compared with prior studies exploring glomerular disease epidemiology in the United States, our study has some notable differences. First, white and black races were both well represented in our cohort, differing from studies that focused almost exclusively on white patients (9). Second, we included all age groups, unlike studies focusing only on adults (12,22). Third, we examined systemic causes of glomerular disease (*e.g.*, lupus nephritis, ANCA/pauci-immune GN, and diabetic glomerulosclerosis) in addition to so-called primary glomerular diseases to capture a wide spectrum of patients undergoing kidney

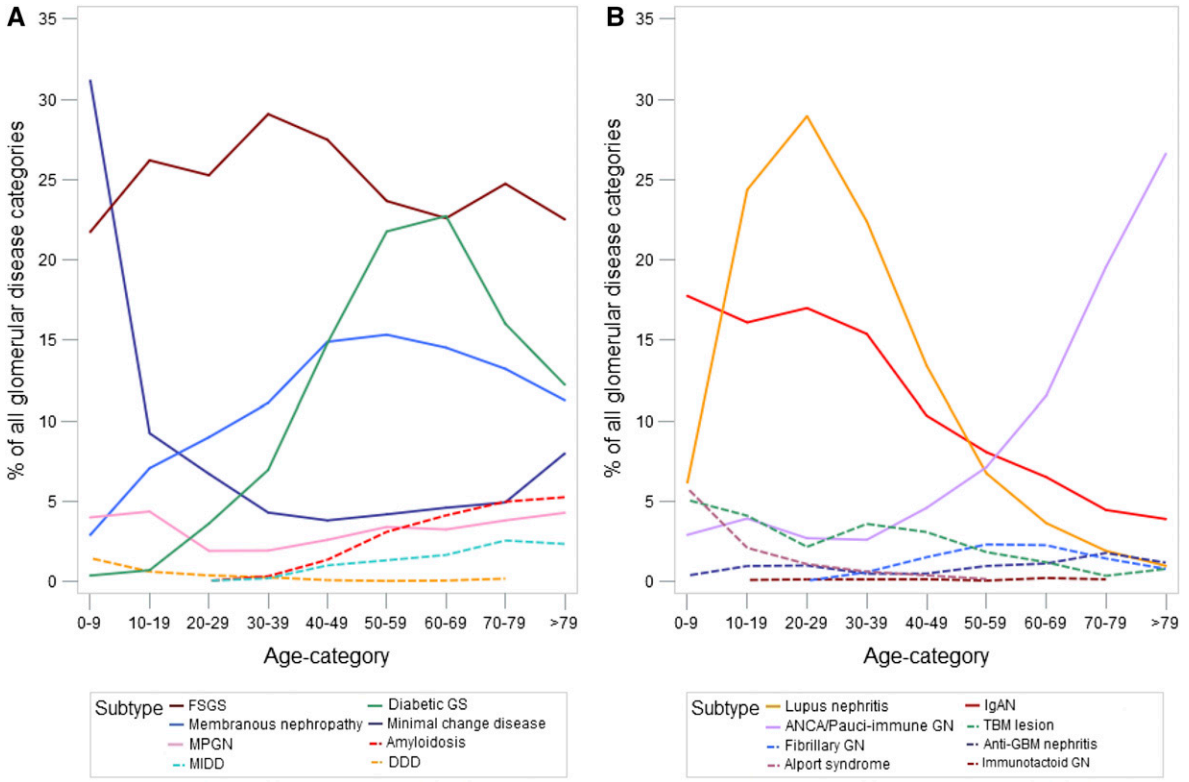

Figure 4. | **Relative renal biopsy diagnosis frequencies of the most common glomerular disease subtypes according to patient age category and typical mode of clinical presentation.** (A) nephrotic syndrome; (B) nephritic features. DDD, dense deposit disease; GBM, glomerular basement membrane; GS, glomerulosclerosis; IgAN, IgA nephropathy; MIDD, monoclonal immune deposition disease; MPGN, membranoproliferative GN; TBM, thin basement membrane.

biopsy for evaluation of suspected glomerular disease. This differs from prior studies limited to patients with nephrotic syndrome (7,8), proteinuria in excess of 2 g/24 h (5), or a more restricted set of primary glomerular disease diagnoses (6,8,22,23). Both of the prior studies that included a wide spectrum of primary and secondary glomerular diseases (9,12) excluded patients with diabetic glomerulosclerosis, prompting our decision to analyze our data with and without diabetic glomerulosclerosis to facilitate comparisons with these studies (our conclusions were unaltered). Fourth, our study is the largest and most contemporary to date; with the exception of two much smaller studies published earlier this year (12,22), recent reports of United States glomerular disease epidemiology are lacking.

Despite these differences, many of our findings support those previously reported. The marked increase in FSGS frequency previously identified at the end of the 20th century (5–9), particularly among blacks, was again seen in our patient cohort. However, our study is the first to show a plateau and subsequent decline in FSGS frequency more recently; unlike a smaller study (n=204) that reported a predominance of membranous nephropathy over FSGS among all racial groups in a contemporary (2001–2011) patient cohort (10), FSGS remained the most frequent glomerular disease subtype in all racial groups in our study. Whether the recent decline in FSGS frequency represents a reduction in patients with primary/idiopathic cases, patients with secondary (*e.g.*, obesity-related) cases, or the likelihood to biopsy a patient with proteinuria could not be discerned from our data.

The rapid and steady increase in the frequency of diabetic glomerulosclerosis that we observed has not, to our knowledge, previously been reported. We propose that this finding largely reflects a true increase in disease incidence, mirroring the increase in diabetes mellitus incidence observed in the United States over the same time interval (24). Additionally, an increasing tendency to biopsy older patients or search for nondiabetic glomerular diseases among patients with diabetes (25,26) might underlie these findings.

Considering other glomerular disease subtypes, the declining frequency of membranous nephropathy that we observed was reported by some (5) but not all (7–9,22) prior studies, whereas a stable frequency of IgA nephropathy (5,8,9) and declining frequency of minimal change disease (7–9,22) have more consistently been observed. With respect to the declining frequency of minimal change disease, pediatric nephrologists might be more inclined to empirically treat children with nephrotic syndrome, obviating the need for a kidney biopsy, in more recent decades; however, this would not explain the decline in minimal change disease frequency in middle-aged and older adults. With respect to the declining frequency of membranous nephropathy, we do not expect that testing for antiphospholipase A2 receptor antibodies has yet replaced the role of kidney biopsy in this disease group.

Thus, we consider declines in the relative frequencies of these diagnoses to be most likely due to true declines in disease incidence. Descriptions of temporal trends in several more rare glomerular disease subtypes are also novel to our study.

In addition to reporting temporal trends, we also confirm some previously described demographic predispositions to glomerular disease development (*e.g.*, a higher risk for IgA nephropathy in younger white or Asian patients [23] and a higher risk for lupus nephritis in younger black patients or women [27]) in a large and contemporary United States cohort. We also comprehensively analyzed glomerular disease frequencies according to several combinations of demographic factors and typical modes of glomerular disease presentation (nephrotic versus nephritic), which may serve as useful resources to clinicians evaluating patients in the clinic or researchers aiming to target high-risk patient groups for inclusion in future translational research studies or interventional trials.

Our study has several limitations. We had too few Latino and Asian patients to enable analysis of temporal trends or demographic associations in these racial/ethnic groups. We could not precisely determine our referral population size and thus, report relative (not absolute) incidences. We estimate that the Division of Nephropathology at the UNC biopsies derive from a population of approximately 10 million people, although accurate estimates of population sizes over time could not be determined.

To conclude, we identified in a large, contemporary United States population that the frequencies of many glomerular disease subtypes have shifted considerably over the past three decades. We provide evidence that changes in population demographics (age, sex, or race) contributed minimally to these findings and instead, propose that environmental and lifestyle changes most likely underlie them. Of particular concern was the dramatic increase in the frequency of diabetic glomerulosclerosis that we observed given the adverse outcomes (28) and increased health care costs (29) associated with this diabetic complication. On a more encouraging note, the relative (and in some cases, absolute) frequencies of some other glomerular disease subtypes declined. We propose that further exploration of the underlying reasons for these epidemiologic shifts is warranted and that these efforts might reveal novel insights into disease pathogenesis or therapeutic opportunities.

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Disclosures

None.

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