

## Supplemental Materials

**Supplemental Table 1: Characteristics of patients with secondary FSGS with identifiable risk factor(s) vs secondary FSGS without identifiable risk factor(s)**

**Supplemental Table 2: Treatment and renal outcomes for patient with focal segmental glomerulosclerosis**

**Supplemental Figure 1: Overview of study design.**

**Supplemental Figure 2: Correlation between proteinuria and foot process effacement in patients with primary FSGS (red squares) and secondary FSGS (blue diamonds).** All patients with primary FSGS had proteinuria > 3.5 g/day. However, patients with secondary FSGS had proteinuria that ranged from 46 mg/day to 11 g/day. Pearson's correlation coefficient (R) for correlation between the degree of foot process effacement and proteinuria was 0.41,  $P=.008$  for the total cohort.

**Supplemental Figure 3: Trends in the incidence rates of kidney biopsy, glomerular diseases and focal segmental glomerulosclerosis in Olmsted County over the period of 1994-2013.** Using Poisson regression models, estimated native kidney biopsy incidence rates increased significantly from 1994-2003 to 2004-2013 (17% increase per 5 years,  $P<.001$ ). The incidence of glomerular diseases also increased during the same time period but was not statistically significant (11% increase per 5 years,  $P=.05$ ). Incidence of focal segmental glomerulosclerosis increased significantly over the same time period (41% increase per 5 years,  $P=.02$ ).

**Supplemental Figure 4: Trends in the incidence rates of kidney biopsy, focal segmental glomerulosclerosis and all subtypes of glomerular diseases in Olmsted County over the period of 1994-2013.** Abbreviations: FSGS, focal segmental glomerulosclerosis; Global GS, global glomerulosclerosis; GN, glomerulonephritis; IgA, Immunoglobulin A Nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis. Other included cases of amyloidosis, Fabry's disease, Fibrillary glomerulonephritis, HIV-associated nephropathy, infection-associated glomerulonephritis, monoclonal gammopathy of renal significance, thrombotic microangiopathy.

**Supplemental Table 1: Characteristics of patients with secondary FSGS with identifiable risk factor vs secondary FSGS without identifiable risk factor**

Characteristic	Secondary FSGS with identifiable risk factors <sup>a</sup> N=13	Secondary FSGS without identifiable risk factors N=21	P value
	Mean (SD) or N(%)	Mean (SD) or N(%)	
<b>Demographics</b>			
Age, yr	47 ± 20.4	55 ± 18.1	.30
Male	3 (23%)	15 (71%)	<b>.01</b>
White	11 (85%)	15 (71%)	.44
<b>Clinical characteristics at time of biopsy</b>			
SBP at time of biopsy, mmHg	131 ± 28.1	141 ± 20.1	.79
DBP at time of biopsy, mmHg	77 ± 17.4	80 ± 15.9	.62
BMI, kg/m <sup>2</sup>	29.7 ± 8.6	32.9 ± 6.7	.11
Comorbidities			
HTN	9 (69%)	19 (90%)	.17
DM	2 (15%)	7 (35%)	.26
Vascular disease <sup>b</sup>	4 (40%)	6 (30%)	.69
Dyslipidemia	5 (38%)	12 (57%)	.48
BMI > 30	4 (31%)	13 (68%)	.07
<b>Medications at time of biopsy</b>			
ACEi/ARB	6 (46%)	14 (67%)	.30
Statins	5 (38%)	12 (57%)	.48
<b>Laboratory data at time of biopsy</b>			
Serum creatinine mg/dl			
Median (IQR)	1.4 (1.05-2.1)	1.45 (1.05-2.3)	.79
Albumin, g/dl	3.9 ± 0.3	4.1 ± 0.3	.06
Proteinuria, g/day	2.8 ± 1.8	3.4 ± 3.1	.92
Total cholesterol, mg/dl	219 ± 85.7	213 ± 50.4	.86
<b>Biopsy characteristics</b>			

Number of glomeruli	19 ± 15.0	12 ± 7.5	.26
% Globally sclerotic glomeruli	27% ± 24	48% ± 24	<b>.02</b>
Globally sclerotic glomeruli abnormal for age			
Interstitial fibrosis >5%	13 (100%)	18 (86%)	.27
Interstitial fibrosis >25%	2 (15%)	10 (48%)	.08
Arteriosclerosis 0-3 <sup>c</sup>	1.2 ± 1.0	1.3 ± 1.1	.74
Arteriolar hyalinosis 0-3 <sup>c</sup>	0.9 ± 1.1	1.3 ± 1.1	.31
Foot process effacement	43% ± 32	38% ± 28	.65

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate using creatinine-based CKD-EPI equation; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; SBP, systolic blood pressure

<sup>a</sup>Risk factors of secondary FSGS included: included reflux and obstructive uropathy (N=3), confirmed genetic FSGS (N=1), previous nephrectomy or dysplastic kidney (N=2), renal artery stenosis (N=1), thin basement membrane disease (N=2), history of pre-eclampsia (N=2), pamidronate (N=1), and chronic lithium use (N=1)

<sup>b</sup>vascular disease is composite of coronary artery disease, stroke or peripheral arterial disease

<sup>c</sup>scale 0-3 with 0=none, 1=mild, 2=moderate, 3=severe

**Supplemental Table 2: Treatment and follow-up of patient with FSGS**

	<b>Primary FSGS N=12</b>	<b>Secondary FSGS N=34<sup>a</sup></b>	
	<b>Immunosuppression N=4</b>	<b>Conservative N=8</b>	<b>Conservative N=32</b>
	<b>Mean ± SD or N(%)</b>	<b>Mean ± SD or N(%)</b>	<b>Mean ± SD or N(%)</b>
Treated with ACEi/ARB after biopsy	4 (100%)	6 (75%) <sup>b</sup>	27 (84%) <sup>c</sup>
Baseline proteinuria, g/day	10.0 (3.7)	7.0 (2.8)	3.1 (2.8)
Proteinuria at 6 months post biopsy, g/day	3.3 (2.9)	2.6 (2.1)	2.2 (2.1)
Mean difference in proteinuria after treatment, g/day	-8.1 (3.3)	-4.6 (0.7)	-1.3 (0.4)
Progressing to ESRD (%) <sup>d</sup>	1 (25%)	3 (38%)	10 (32%)
Progressing to ESRD or 40% decline in eGFR (%)	2 (50%)	5 (63%)	20 (63%)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate

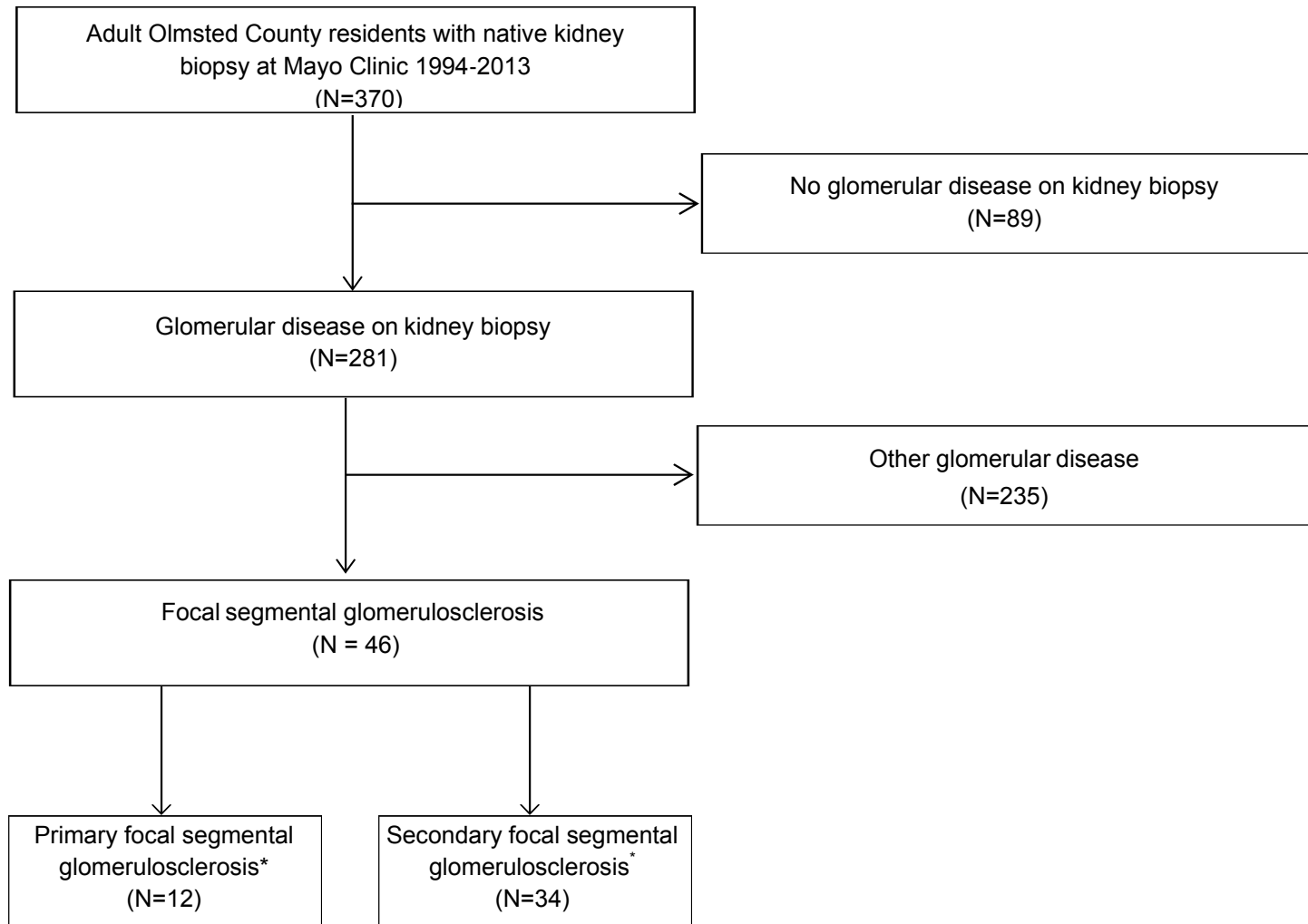
using creatinine-based CKD-EPI equation; ESRD, end-stage renal disease;

<sup>a</sup>Two patients treated with immunosuppressive therapy.

<sup>b</sup>Two patients did not receive ACEi or ARB due to advanced CKD at the time of biopsy.

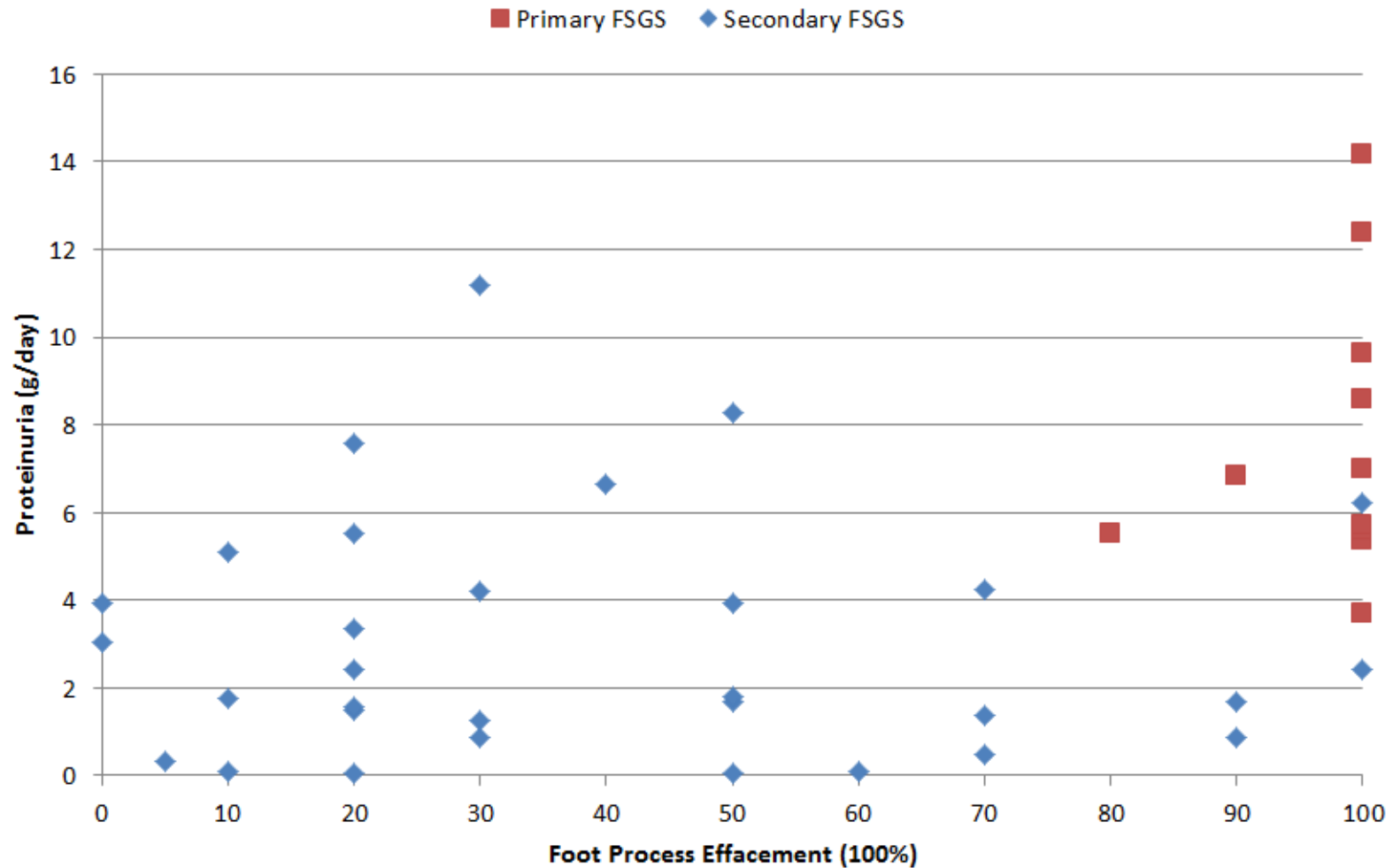
<sup>c</sup>Five patients treated with blood pressure control without ACEi or ARB due to the following reasons: minimal proteinuria (n=1), advanced CKD (n=1), unclear reasons (n=3).

<sup>d</sup>Mean time to progression to ESRD for patients with primary FSGS was 6 months vs 4.5 years for patients with secondary FSGS ( $P=.03$ ).

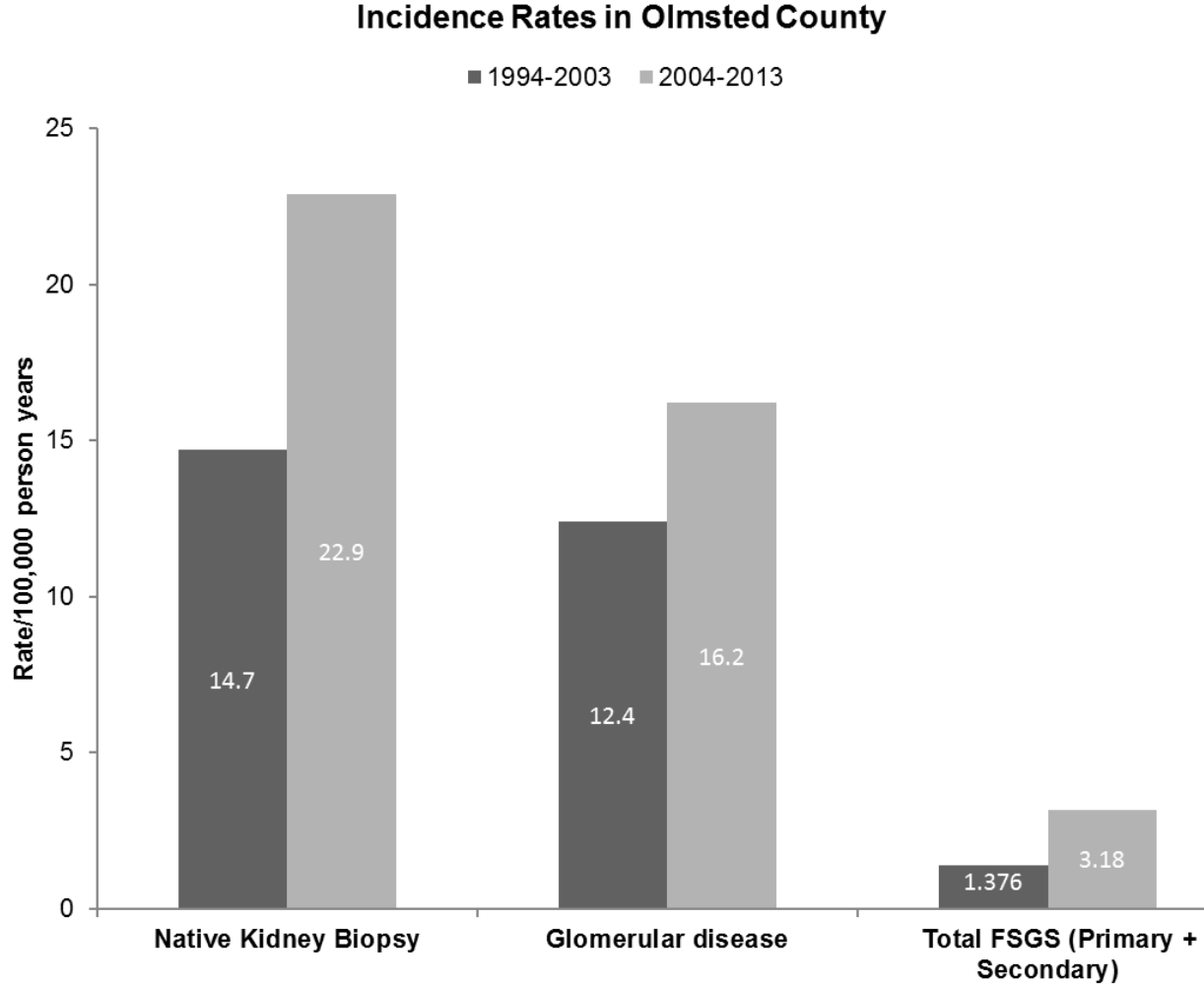


**Supplemental Figure 1: Overview of study design.** \* Primary focal segmental glomerulosclerosis was defined as foot process effacement  $\geq 80\%$  without identifiable cause. All other patients were classified as secondary focal segmental glomerulosclerosis. Four patients without available electron micrographs were classified based on their clinical presentation.

## Relation between Proteinuria and Foot Process Effacement

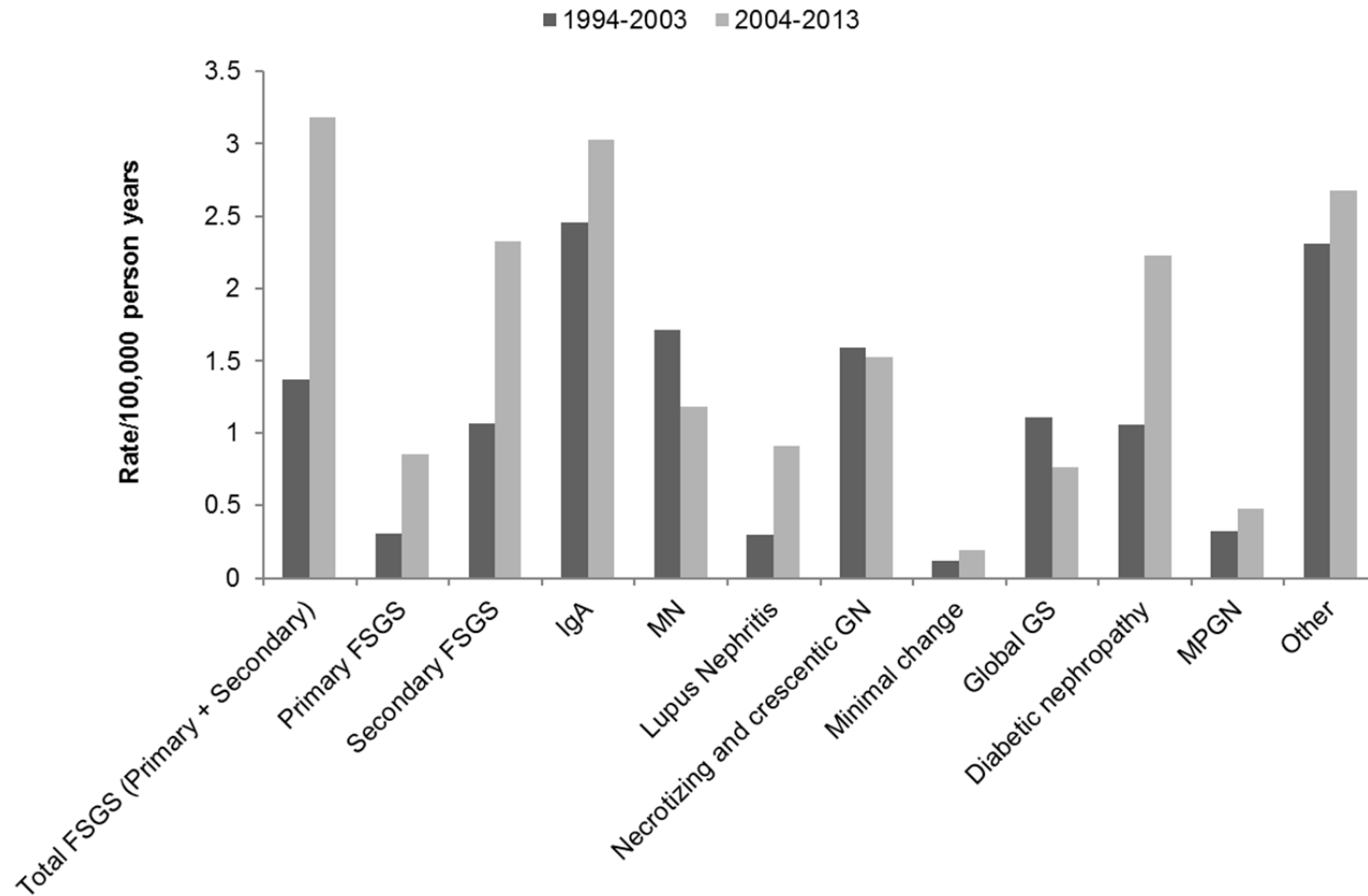


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## Incidence Rate of Glomerular Disease in Olmsted County



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