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Studying glomerular disease epidemiology: tackling challenges and paving a path forward

A thesis submitted to University College Cork for the degree of Doctoratus in Medicina (MD) in the School of Medicine

Michelle Marie O'Shaughnessy

MB BCh BAO MS FRCPI FASN

Head of School: Prof. Paula O'Leary

Thesis Supervisors: Prof. Joe Eustace and Dr. Frances Shiely

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Contents

List of abbreviations

ADPKD, autosomal dominant polycystic kidney disease

ERKNet, European Reference Network for Rare Kidney Disease

ESRD, end-stage renal disease

FSGS, focal segmental glomerulosclerosis

GDCN, Glomerular Disease Collaborative Network

GN, glomerulonephritis

GS, glomerulosclerosis

HRB-CRF, Health Research Board – Clinical Research Facility

IgAN, immunoglobulin A nephropathy

IKBS, International Kidney Biopsy Survey

LN, lupus nephritis

MN, membranous nephropathy

MPGN, membranoproliferative glomerulonephritis

UCC, University College Cork

USRDS, United States Renal Data Service

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

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Dec 22nd, 2020

Abstract

Background: Glomerular diseases are a group of rare immune-mediated kidney diseases that affect the glomeruli, or filtering units, of the kidney. Major knowledge gaps remain in our understanding of glomerular disease epidemiology. Efforts to describe glomerular disease distributions based on geographic, demographic, and temporal factors (descriptive epidemiology) are limited by the absence of population-level disease registries in most jurisdictions. The extent to which glomerular disease subtype independently associates with clinical outcomes (analytic epidemiology), especially once kidney disease has progressed to end-stage kidney failure, remains largely unknown. Further, much of what is known regarding glomerular disease epidemiology is derived from the experiences of highly-selected patient populations enrolled in clinical trials or attending academic medical centres. Larger-scale, population-level, studies of glomerular disease epidemiology would help to close knowledge gaps regarding the distribution and determinants of glomerular disease and, in doing so, would inform clinical care, public health policy, and clinical trial design.

Hypotheses: Two major hypotheses are explored in this thesis: 1. Significant geographic and temporal variation in glomerular disease frequencies exist, that are not solely explained by racial-ethnic variation, thus supporting a role for socioeconomic and environmental factors in the development of clinically manifest glomerular disease; 2. Glomerular disease subtype independently associates with clinical outcomes even after glomerular disease has advanced to end-stage kidney failure, challenging the prevailing paradigm to group all glomerular disease subtypes together in research and public health reporting of clinical outcomes in patients with end-stage kidney failure.

Aims: The overall aim of this research was to close knowledge gaps in glomerular disease epidemiology by identifying geographic and temporal variation in glomerular disease frequency distributions and by determining associations between glomerular disease subtype and clinical outcomes (mortality, cardiovascular events) in patients with end-stage kidney failure.

Methods: For the first two manuscripts (**Chapters 3 and 4**), I analysed two large-scale pathology datasets created by my collaborator, Dr. Charles Jeannette: a) the International Kidney Biopsy Survey (IKBS) that includes kidney biopsy diagnoses and associated patient demographics from 29 international kidney pathology laboratories, which I used to study geographic variation in glomerular disease frequencies within and across racial-ethnic groups; b) the Glomerular Disease Collaborative Network (GDCN), a registry of all kidney biopsies referred to the University of North Carolina since 1986, which I used to study temporal trends in glomerular disease frequencies within and across

demographic groups over the last three decades. For the next two manuscripts (**Chapters 5 and 6**), I analysed data – including physician-reported cause of kidney failure – from virtually all U.S. patients with treated end-stage kidney failure who are enrolled, by federal mandate, in the United States Renal Data System (USRDS). In the first of these two manuscripts, I determined associations between glomerular disease subtype and mortality; in the second, I determined associations between glomerular disease subtype and cardiovascular events. Advanced statistical methods included multivariable regression to handle confounding, proportional sub-distribution hazard models to handle competing events, and multiple imputation to handle missing data.

Results: Major findings from these manuscripts include: a) significant differences in glomerular disease frequencies across continents, even among patients with similar racial-ethnic backgrounds; b) significant temporal trends in the relative frequencies of many biopsy-proven glomerular diseases, including stabilization in the 21st century of the rapid increase in focal segmental glomerulosclerosis observed at the end of the 20th century, and a dramatic increase in diabetic glomerulosclerosis over time, to become the second most frequent biopsy-proven glomerular disease diagnosis in the modern era; c) significant differences in the hazards of mortality and cardiovascular events across glomerular disease subtypes, even after accounting for between-group differences in case-mix.

Conclusions: In addition to answering specific research questions regarding glomerular disease epidemiology, this research exemplifies the strengths and feasibility of population-level, internationally collaborative, approaches to studying glomerular diseases. Findings from these studies can shape public health policy (e.g. promotion of healthy lifestyle approaches to curb the high frequency of diabetic glomerulosclerosis in contemporary U.S. populations), future research design (e.g. recognising the importance of glomerular disease subtype as a prognostic indicator in studies involving patients with end-stage kidney failure), and clinical care (e.g. formulating differential diagnoses based on patient demographics, or counselling U.S. patients regarding their absolute and relative risks of mortality and cardiovascular events following dialysis initiation).

Preface

The research reported in this thesis was conducted while I underwent fellowship training at Stanford University from 2013 to 2016. My training in glomerular disease included a 6-week visit as an academic scholar to the University of North Carolina, Chapel Hill, a world-renowned centre of excellence for glomerular disease research and clinical care, where I devised the first two projects presented in this thesis. My training in epidemiology and statistical methods included completion of a Master of Science degree in Epidemiology and Clinical Research at Stanford University, from which I graduated in January 2016 with a perfect Grade Point Average of 4.2. I was supervised during the conduct of this work by my research mentors Drs. Wolfgang Winkelmayer, Susan Hogan, and Maria Montez-Rath. I independently performed all statistical analyses, including generation of figures and tables, for the first two manuscripts (**Chapters 3 and 4**); I received support from a biostatistician when performing the advanced statistical techniques required for the third and fourth manuscripts (**Chapters 5 and 6**). I was first author for all four manuscripts and, in this role, was primarily responsible for study design, statistical analyses, interpretation of research output, and manuscript writing. All four manuscripts have already been published in an academic peer-reviewed journal.

After completing my fellowship training, I next joined the Nephrology Faculty at Stanford University as an Assistant Professor (2016-2019), before returning to Ireland to take up a position as a Consultant Nephrologist at Cork University Hospital and Clinical Senior Lecturer at UCC, in January 2020. In addition to maintaining my role as an investigator with two North American glomerular disease clinical research networks (NEPTUNE,[1] CureGN[2]), I am establishing a Glomerular Disease Centre at Cork University Hospital, which I aim to have approved as a Reference Centre for glomerular disease care within the European Reference Network for Rare Kidney Diseases (ERKNet)[3].

My research mentors and collaborators since returning to Ireland include Prof. Joe Eustace, Consultant Nephrologist and Director of the Health Research Board's Clinical Research Facility (HRB-CRF) at UCC, and Dr. Frances Shiely, Director of Education for the HRB-CRF and Programme Director for the MSc degree in Clinical Trials (UCC), who together supervised my preparation of this thesis. I particularly wish to acknowledge their assistance with selecting manuscripts to include in the thesis as well as their careful review and editing of the introduction and discussion sections of this thesis.

Chapter 1. Introduction

1.1. Chapter overview

This chapter will provide context for the four manuscripts presented in this thesis, by: explaining the terms glomerular disease and epidemiology; reviewing relevant background literature relating to glomerular disease epidemiology; and presenting the overarching and specific aims for this research.

1.2. What are glomerular diseases?

Glomerular diseases are a group of immune-mediated kidney diseases that affect the glomeruli, or filtering units, of the kidney. They can be kidney-limited (primary glomerular diseases) or affect the kidney as part of a systemic disease process (secondary glomerular diseases).[4] Glomerular diseases typically damage the kidney filters, resulting in leakage of blood and/or protein in to the urine and, in many cases, a slowly progressive or more rapid decline in kidney function leading to end-stage kidney failure. In the acute phase, glomerular diseases can also result in the nephrotic syndrome, defined by heavy protein leakage in the urine, low albumin levels in the blood, and oedema (fluid retention),[4] with a propensity to develop hypercholesterolemia,[5] thrombotic events,[6-8] and infection[9].

Many different subtypes of glomerular disease exist. These are primarily distinguished from one another based on histologic findings by kidney biopsy, although diagnoses are further refined based on clinical features (e.g. pathologic triggers, markers of disease severity).[10,11] The treatment of glomerular diseases typically includes immunosuppressive therapies,[4] although some patients can enter remission spontaneously, or forego immunosuppressive treatments if risks are expected to outweigh benefits.

1.3. What is epidemiology?

Epidemiology refers to the study of the distribution and determinants of disease in specified populations, and the application of this study to the control of health problems.[12] Studying disease distributions is termed “descriptive epidemiology”, and involves determining the incidence and prevalence of disease in certain populations i.e. asking “who?”, “what?”, “where?”, “when?”, and “how often?”. Studying disease determinants is termed “analytic epidemiology”, and involves elucidating the causes and consequences of disease i.e. answering “why?”.

As outlined in a recent editorial by this author, an epidemiologic approach is particularly well suited to the study of diseases lacking a single root cause, in which a constellation of genetic, epigenetic, demographic, and environmental factors converge to enable disease expression.[13] In this context, epidemiologic studies can help to tease apart the relative contributions of each of these factors to disease incidence and outcomes. The resulting new knowledge can then be applied to:

- **Public health:** e.g. quantifying the overall burden of disease; identifying high risk patient groups to be targeted in screening strategies, healthcare initiatives, and research funding.

- **Patient care:** e.g. refining differential diagnoses based on patient demographics; counselling patients regarding their predicted prognosis; personalising treatments to patient profiles.

- **Clinical trial design**: e.g. generating hypotheses to test in interventional studies; identifying target populations to be studied (e.g., those with the highest disease incidence or greatest risk for adverse outcomes); determining trial feasibility (i.e., realistic recruitment targets).

1.4. Challenges to studying glomerular disease epidemiology

Studying glomerular disease epidemiology poses many challenges, which I aimed to overcome in the body of work presented in this thesis.

1.4.1. Disease rarity

Although the true incidences of individual glomerular diseases remain to be defined, best estimates support their designation as rare diseases, with an incidence of less than 5 per 10,000 person years.[14] Reflecting this, "immune-mediated glomerulopathies" was included as one of 28 working groups for the recently formed European Reference Network for Rare Kidney Diseases (ERKNet).[3]

When studying the distribution and determinants of rare disease, single-centre studies typically include too few patients to facilitate population-level inferences. Reports emanating from large academic centres also have limited generalisability, as patient characteristics, treatment patterns, and outcomes, are unlikely to reflect real world patient experiences.[15-19] Opportunities to study larger, more representative, patient cohorts are urgently required, to produce internally and externally valid findings.

Approaches taken to overcome this challenge: This thesis includes analyses of some of the largest cohorts of patients with glomerular disease ever described, including: 42,603 glomerular disease diagnoses from 18 countries as part of the International Kidney Biopsy Survey; 22,516 patients with a kidney biopsy specimen showing glomerular disease referred to the University of North Carolina, Chapel Hill; 84,301 patients with end-stage kidney failure attributed to glomerular disease who initiated dialysis or received a kidney transplant in the U.S. between 1996 and 2011; and 63,656 patients with end-stage kidney failure attributed to glomerular disease who initiated dialysis in the U.S between 1997 and 2014. The sheer magnitude of these patient populations enabled findings identified in the full patient cohort to be studied within demographic sub-groups (with sufficient statistical power), for geographic variation and temporal trends in even the rarest of glomerular disease subtypes to be studied, and for the application of advanced statistical methods to enhance the internal validity of study findings.

1.4.2. Difficulty identifying cases using traditional structured clinical research datasets

Administrative diagnostic codes are frequently used to identify patients with diseases of interest from electronic healthcare records or insurance claims data, to support clinical outcomes research. However, as is the case for many rare diseases,[20] diagnostic codes for glomerular disease insufficiently map to clinically used glomerular disease terminologies. Further, diagnostic biomarkers (such as haemoglobin A1C in the case of diabetes) are lacking for most glomerular diseases, and instead a kidney biopsy is required to make a definitive diagnosis. However, kidney biopsy reports are either absent from clinical research datasets or are only available as manually-searchable free text documents, precluding their use as a means to rapidly identify cases of interest.

Determining ways to readily and reliably identify patients with glomerular disease from electronic healthcare records or health insurance claims datasets (e.g. by developing and validating algorithms to identify cases using administrative codes, or by using natural language processing to extract diagnoses from free-text biopsy reports) would advance the ability to study glomerular disease epidemiology at the population level. At the same time, opportunities to study existing diverse datasets that reliably identify patients with glomerular disease by other means should also be harnessed.

Approaches to overcome this challenge: To overcome this challenge, I identified two pathology datasets, described in **Chapters 3 and 4**, in which cases of glomerular disease were confirmed by kidney biopsy, obviating the need to rely on clinical data alone. For **Chapters 5 and 6**, I relied upon glomerular disease diagnoses submitted to the USRDS by patients' treating physicians; while confirmatory biopsy

data are not provided, a prior validation study examined the precision and reliability of glomerular disease designations in the USRDS and determined them to be poorly sensitive but highly specific.[21]

Beyond the scope of this thesis, I also developed reliable algorithms to identify patients with glomerular disease from electronic healthcare records, using combinations of administrative diagnostic codes.[22,23] I am also developing an approach to reliably identify patients with membranous nephropathy using natural language processing methods applied to free text kidney biopsy reports (work in progress).

1.4.3. Characteristically slow clinical course

The most definitive outcomes in kidney disease are death and kidney failure. However, it can often take years or even decades for these outcomes to occur.[24] Among patients recruited to prospective glomerular disease registries or clinical trials, very few might develop these outcomes over the first few years of follow-up. Surrogate outcomes (e.g. change in kidney filtering function or protein excretion in the urine) have more recently been validated and accepted for use in kidney disease clinical trials.[25] It is reasonable to apply these surrogate outcomes to observational studies also. However, the absolute risk for, and time to, kidney failure or death cannot readily be extrapolated from surrogate outcome data, nor can these findings be easily communicated to patients, limiting their clinically applicability.

An ability to study definitive longer-term clinical end-points, including death and cardiovascular events, would greatly contribute to the existing literature regarding glomerular disease epidemiology.

Approaches to overcome this challenge: By using the USRDS, a national registry of all patients with treated end-stage kidney failure in the U.S., I could study long-term clinical outcomes for patients who initiated dialysis or received a kidney transplant in the U.S. since 1996. Data linkage to transplant, death, and Medicare claims records allowed complete capture of major clinical endpoints of interest.

1.5. Literature review of relevant studies

A detailed systematic review of all prior studies examining glomerular disease epidemiology in the U.S. and internationally is beyond the scope of this thesis. Instead, findings of relevance to the manuscripts presented in this thesis are summarised in the sections below as well as in **Chapters 3 to 6.**

1.5.1. General overview of studies examining glomerular disease frequency distributions among patients undergoing kidney biopsy

In the past decade, major breakthroughs in our understanding of the biological mechanisms underlying glomerular disease have occurred, including the discovery of genetic risk alleles predisposing to the development of focal segmental glomerulosclerosis (FSGS) in patients of African ancestry,[26] and pathogenic auto-antibodies that serve as diagnostic and prognostic biomarkers in membranous nephropathy.[27] However, the roles that demographic, socioeconomic, and environmental factors play in conferring disease risk, and modifying disease expression, remain poorly understood.

Examining demographic, geographic, and temporal differences in glomerular disease frequency distributions in patients undergoing a kidney biopsy is one potential approach to untangle the contributions from these factors to disease risk. However, prior such studies have had limitations:

Non-representative referral populations: Many published reports of glomerular disease frequencies, particularly in the U.S., are restricted to patients attending academic medical centres.[28-30] These cohorts are likely to be enriched for rarer, more severe, or more complex cases. Other studies describe glomerular disease frequencies among socioeconomically or geographically non-representative populations: for example, patients with private insurance living in Southern California.[31]

Inconsistent study inclusion criteria: While some studies report diagnoses from all kidney biopsies performed at or referred to their centre,[32,33] others are restricted to cases with confirmed glomerular disease,[34] or to those with heavy proteinuria.[28,29] Further, some reports include all forms of glomerular disease,[35,36] whereas others are restricted to primary, kidney-limited, forms of glomerular disease.[31,37] This methodological variation largely precludes direct comparisons of findings across studies.

Inconsistent disease nomenclature: Many, particularly older, studies used outdated or non-specific disease nomenclature when categorising glomerular diseases. For example, one study examining temporal trends in glomerular disease incidence in Finland assigned patients to disease categories such as focal proliferative glomerulonephritis (GN), extracapillary GN, endocapillary GN, mesangial non-specific GN, or non-specific GN, none of which map well to clinically used glomerular disease terminologies.[38] Studies that include large numbers of patients assigned to such non-specific diagnoses will under-represent true pathologic entities, and distort inter-study comparisons.

Small sample size: The majority of reports describing glomerular disease frequency distributions among patients undergoing kidney biopsy emanate from single centres and include only a few hundred

patients.[14,39] Particularly for the rarest of glomerular disease subtypes, small sample sizes preclude meaningful analyses of geographic variation or temporal trends in disease frequencies.

Older era: Most prior studies reporting glomerular disease frequency distributions were more than a decade old when the manuscripts presented in **Chapters 3 and 4** were published. [14,39] Glomerular disease frequency distributions in the contemporary era, and the extent to which trends observed at the end of the 20th century continued in to the 21st century, remained largely unknown.

1.5.2. Demographic, environmental, and socioeconomic factors associated with glomerular disease frequency distributions

Prior reports describe significant associations between demographic (age, sex, and race), environmental, and socioeconomic factors, and risk for glomerular disease development.

Age: One of the largest (n=1147) kidney biopsy studies to date, that included both adults and children, reported that glomerular disease frequency distributions differed significantly by patient age: FSGS was most frequent in children under 5 years of age, lupus nephritis in children aged 5 to 14 years, and IgA nephropathy in children and adults 15 years and older.[40] However, most other studies did not report disease distributions within age-defined sub-groups, or excluded children entirely.

Sex: Multiple studies have demonstrated a male preponderance for most of the more common primary and secondary glomerular disease subtypes, with the exception of lupus nephritis.[40-42] However, glomerular disease frequency distributions stratified by patient sex are seldom reported, and sex associations for particularly rare glomerular disease subtypes remain to be defined.

Race: Racial predispositions to glomerular disease development are consistently observed. The increased risk for FSGS in people of African ancestry is at least in part due to a higher prevalence of ApoL1 risk alleles [26] Genome wide association studies have also helped to explain some of the increased risk for IgA nephropathy observed in Asian populations.[43] However, genetic factors do not entirely explain associations between race-ethnicity and glomerular disease frequency distributions: socioeconomic, environmental, and lifestyle factors are also likely to play an important role.[44]

Environmental and socioeconomic factors: At least two reports have described associations between lower socioeconomic status and increased risk for the development of certain glomerular diseases.[45,46] However, neither report delved deeply in to specific factors that might explain this finding. Potential

explanations might include: a direct contribution from lifestyle factors to the development of diabetic nephropathy, obesity related FSGS, or smoking related nodular glomerulosclerosis;[47] a recently reported association between air pollution and increased risk for membranous nephropathy;[48] or purported associations between poor sanitation and higher risk for infection-related glomerular disease but lower risk for autoimmune glomerular diseases[49].

Examining international variation, and temporal trends, in glomerular disease frequency distributions – overall, and within racial-ethnic sub-groups – might help to disentangle the influences of fixed genetic factors from modifiable environmental and socioeconomic factors on disease risk.

1.5.3. International variation in glomerular disease frequencies

Incidence estimates for individual glomerular disease subtypes vary internationally. For example, the incidence of IgA nephropathy was reported to be higher in Victoria, Australia, in both males and females (5.7 and 2.9 per 100,000 person years, respectively)[40] than the overall incidence in Olmsted County, Minnesota (2.1 per 100,000 person years)[30]. In general, IgA nephropathy is the dominant glomerular disease subtype in Europe,[50-54] Australia/New Zealand,[40] and South East Asia,[55,56] while FSGS predominates in some,[28,29,33,57-59] but not all,[30,60] biopsy cohorts in the Americas. Whether international variation in the frequency of biopsy-proven glomerular disease relates to true differences in disease incidence (due to differences in race-ethnicity, socioeconomic, or environmental factors) vs. differences in disease detection (i.e. threshold to perform, or access to, kidney biopsy), remains to be determined.

To our knowledge, only two studies have attempted to systematically compare glomerular disease frequencies across countries and continents. The first examined 40 studies published between 1980 and 2010 reporting the incidence of primary GN in Europe, North and South America, Canada, Australasia and the Middle East.[14] This study was restricted to primary glomerular disease subtypes and did not attempt to compare geographic variation within specific demographic sub-groups. The authors commented on variability in disease nomenclature, which forced them to exclude some reports from their analysis. They also conceded that "most studies were from the USA and France; therefore, it is difficult to draw conclusions regarding variability of rates with geographical location or ethnicity."

The second study compared temporal trends in primary glomerular disease frequencies in Singapore to international trends.[39] The findings from Singapore were difficult to interpret, as non-specific histologic patterns (e.g. mesangial proliferative GN and crescentic GN) were included as diagnoses. However,

when reporting on renal biopsy data from 28 countries worldwide, the investigators focused only on primary glomerular diseases, and commented on considerable heterogeneity with respect to disease nomenclature. Although definitive conclusions regarding international variation could not be made, the authors concluded that "the prevalence of primary GN in various countries throughout the world varies depending on the genetic profile of the population as well as their environmental exposure".

Finally, two smaller studies summarised a less comprehensive selection of international studies. These compared the most frequent glomerular disease diagnoses,[61] and the frequency of IgA nephropathy specifically, [38] in different parts of the world.

To our knowledge, no prior study has collected primary data regarding kidney biopsy frequencies from multiple countries, using a systematic approach to disease nomenclature and study design.

1.5.4. Temporal trends in glomerular disease frequencies in the U.S.

An increasing incidence of FSGS was consistently identified in numerous studies examining glomerular disease frequency distributions in the United States at the end of the 20th century.[28-30,33,37] In some, however, this finding was restricted to Black or Hispanic patients,[29,33] suggesting that that the increasing incidence of FSGS among racial-ethnic minority groups might be explained by a disproportionately higher exposure to adverse socioeconomic or environmental factors predisposing to FSGS development in the modern era. At the time the manuscript presented in **Chapter 4** of this thesis was published, only two prior studies, to our knowledge, had followed this trend in to the 21st century, with conflicting findings: one study of 2,501 privately insured patients in Southern California showed a sustained increase in the incidence of FSGS among all racial groups between 2000 and 2011;[31] another of 204 patients in Chicago found that the rising tide of FSGS evident at the end of the 20th century had ceased, and that membranous nephropathy now predominated in all racial groups (2001-2011).[62] However, both of these studies were relatively small and had limited generalisability to the larger U.S. population.

Temporal trends are less consistent across studies for other glomerular disease subtypes, explained by differences in population demographics (e.g. Caucasian,[30] military,[63] or urban-dwelling patients[28]) or clinical inclusion criteria (e.g. nephrotic syndrome[28,29] vs. any glomerular disease[30,64]). Frequencies of especially rare glomerular diseases are seldom reported.

Accordingly, knowledge gaps with respect to temporal trends in glomerular disease frequencies in the United States include: conflicting findings regarding contemporary FSGS trends in the 21st century; poor understanding of the influence of demographic factors on observed trends; and inadequate study of temporal trends for the rarest of glomerular diseases subtypes, due to insufficient sample sizes.

1.5.5. Associations between glomerular disease subtype and clinical outcomes in patients with end-stage kidney disease attributed to glomerular disease

Clinical outcomes in patients with glomerular diseases are notoriously heterogeneous and difficult to predict. One prognostic factor that has been examined in a handful of studies is glomerular disease subtype itself i.e. after accounting for differences in demographics, comorbidities, and disease severity, does glomerular disease subtype have independent prognostic significance? To cite one example, the risk for thromboembolism is reported to be significantly higher in membranous nephropathy than in other forms of glomerular disease, even after accounting for between-group differences in age, sex, serum albumin, and history of malignancy.[6] This finding has influenced clinical practice, by lowering the threshold to provide prophylactic anticoagulation to patients with membranous nephropathy.[4]

However, the degree to which glomerular disease subtype is associated with **mortality** remains to be determined. One single-centre, retrospective study of 580 Taiwanese patients with biopsy-proven GN, not yet requiring dialysis (mean eGFR 70.4 ±33.8 ml/min/1.73m2), reported a lower frequency of comorbidities and less use of cytotoxic medications in patients with IgA nephropathy compared to those with membranous nephropathy or FSGS. Unadjusted mortality, after a median follow-up of 5.9 years, was also significantly lower in IgA nephropathy (4.6%) than in membranous nephropathy (17.2%) or FSGS (14.4%). However, multivariable adjustment for between-group differences in demographics, disease severity, and comorbidities, were not performed; accordingly, whether these differences represent an independent association between glomerular disease subtype and patient mortality, versus the confounding influence of differences in in demographics and renal or non-renal clinical factors, could not be determined. Another similar study of 1,943 Korean patients with primary GN also identified a survival advantage in IgA nephropathy as compared to membranous nephropathy, FSGS, or membranoproliferative GN. Again, however, differences in case-mix were also not considered.

Another area in which there are major knowledge gaps is the degree to which glomerular disease subtype retains prognostic importance once a patient's kidney disease has progressed to **end-stage**

kidney failure. With respect to **mortality** differences, the Taiwanese study cited above did report patient outcomes in the small (n=257) subset of patients from this cohort who developed end-stage kidney failure. In this sub-group, 10-year survival risks of 85%, 80%, 61%, and 26% for IgA nephropathy, membranous nephropathy, FSGS, and membranoproliferative GN, respectively, were reported. However, multivariable adjustment for between-groups differences in demographics and comorbidities were not performed and, thus, whether an independent association exists between glomerular disease subtype and mortality following the onset of kidney failure remains unknown.

With the exception of this sub-group analysis, most other studies reporting **mortality** outcomes after kidney failure development in glomerular disease were restricted to single glomerular disease subtypes,[65,66] or combined subtypes together into a single disease category.[67] Studies directly comparing mortality outcomes across major glomerular disease subtypes were largely lacking.

With respect to **cardiovascular** outcomes, studies restricted to a single glomerular disease subtype have described high rates of cardiovascular events in patients with glomerular disease.[17,68-71] However, either prior to or following the onset of kidney failure, I am not aware of any study that directly compared rates of cardiovascular outcomes across glomerular disease subtypes.

I hypothesised that glomerular disease subtype might independently associate with the clinical outcomes of mortality and cardiovascular events even after patients' kidney disease had progressed to end-stage kidney failure. Any observed differences might in part be explained by confounding (e.g. differences in demographics or comorbidity burden) but in part might relate to factors directly or indirectly caused by the patient's glomerular disease or its treatment, including chronic damage to the vasculature prior to the onset of kidney failure as well as continued nephrotic syndrome, systemic inflammation, or use of immunosuppressive therapies even after the onset of kidney failure.

1.6. Thesis Aims

1.6.1. Overall Aim

The overarching aim of this thesis was to better understand geographic variation and temporal trends in glomerular disease frequencies, as well as associations between glomerular disease subtype and clinical outcomes in patients with end-stage kidney failure.

1.6.2. Specific objectives of the individual manuscripts

1. To determine international variation in glomerular disease frequency distributions, overall and within racial-ethnic subgroups, using data from an international kidney pathology survey that adopted a standardised, contemporary, approach to disease nomenclature **(Chapter 3)**

2. To identify temporal trends in glomerular disease frequency distributions in the South Eastern United States over the last 30 years, overall and within specific demographic sub-groups, using data collected for a prospective glomerular disease registry **(Chapter 4)**

3. To quantify the nature, strength, independence, and significance of relationships between glomerular disease subtype and mortality **(Chapter 5)** and cardiovascular outcomes **(Chapter 6)** among U.S. patients with treated end-stage kidney failure.

Chapter 2. Methods Overview

2.1. Chapter overview

Detailed descriptions of individual study methods – including data sources, cohort creation, variable definitions, and statistical approaches – are contained within each of the individual published manuscripts (**Chapters 3 to 6**). In this chapter, I wish to highlight methodological themes that are common to most or all of the included manuscripts, demonstrating the cohesive nature of this work.

2.2. Data sources

To overcome some of the limitations of prior studies examining glomerular disease epidemiology, I employed data sources with the following attributes:

1. A sufficiently large number of cases to allow stratification by age, sex, and race, when examining geographic variation and temporal trends in glomerular disease frequencies

2. Use of pathology datasets that adopted a systematic, consistent, approach to defining and categorising glomerular disease diagnoses, using contemporary disease nomenclature

3. Regionally, nationally, and/or internationally representative patient cohorts, such that study findings are broadly generalisable to real world glomerular disease patient populations

4. Inclusion of all major forms of glomerular disease, both primary and secondary

With these goals in mind, I created some of the largest cohorts of patients with glomerular disease ever described, in whom I could study a series of specific research questions. An overview of the details, strengths, and limitations of each of these data sources are now described.

2.2.1 The International Kidney Biopsy Survey (IKBS)

Description of the data source: The IKBS was designed by my two collaborators, Dr. Charles Jeannette and Dr. Agnes Fogo, with support from the American Society of Nephrology Glomerular Diseases Advisory Group (ASN GDAG), the Renal Pathology Society (RPS), and the European Renal Association—European Dialysis and Transplantation Association (ERA-EDTA) Immunonephrology Working Group.

Centers were invited to participate in the survey between 2012 and 2013 and were asked to provide all consecutive native kidney biopsy diagnoses reported by their kidney pathology laboratory, either retrospectively or prospectively, over a self-selected recent time period of at least one year. Centers were also instructed to report demographic data, if available, as summary values for each diagnosis, including: mean age, minimum age, maximum age, number of males, number of females, and number of patients with each of 4 mutually exclusive race/ethnicity categories (white, black, Asian, or Latino).

Strengths of the data source:

- Inclusion of all consecutive biopsy cases, thus minimising selection bias
- Use of standardised case definitions when assigning diagnoses
- Global representation, with data from 29 centres across 18 countries and 4 continents
- Huge scale, with collection of over 40,000 glomerular disease diagnoses

Limitations of the data source:

- If two or more diagnoses were identified from a single biopsy specimen, each diagnosis was regarded as a separate observation i.e. the unit of measurement was diagnosis, not patient
- Demographic data were provided by the centres at the group and not individual level
- The size and demographic composition of the referral population was only available for two centres, and thus proportional frequencies rather than absolute incidence rates are reported

2.2.1. The Glomerular Disease Collaborative Network (GDCN)

Description of the data source: The GDCN is a large prospective registry of patients with glomerular disease, initiated in 1986 and hosted at the University of North Carolina, Chapel Hill. All biopsies referred to the nephropathology department at UNC Chapel Hill, including those referred from a large catchment area that extends beyond the state of North Carolina, are included in the pathology registry. Some of these patients will also contribute clinical data, although these data were not the focus of this thesis.

Strengths of the data source:

- Complete case capture, minimising selection bias
- Inclusion of patients from the community in addition to those attending academic centres
- Processing of all specimens by light, immunofluorescence and electron microscopy
- Diagnoses made by one of three experienced nephropathologists, who were also involved in the clinical care of patients and could refine histopathologic diagnoses in light of clinical data

Limitations of the data source:

- Could not always distinguish primary from secondary glomerular disease diagnoses (e.g. immune-mediated FSGS from obesity-related FSGS)
- The size and demographic composition of the referral population could not accurately be defined, and thus proportional frequencies rather than absolute incidence rates are reported

2.2.3. The United States Renal Data System (USRDS)

Description of the data source: The USRDS contains records for virtually all patients who receive a kidney transplant or long-term dialysis in the United States. We obtained cause of kidney failure, demographic characteristics, comorbidities, laboratory values, and body mass index (BMI) from *patient* and *medevid* files: these data are derived from Centres for Medicare & Medicaid Services (CMS) Medical Evidence Reports (Form CMS-2728) submitted by nephrologists, by federal mandate, within 45 days of a patient commencing a new ESRD treatment. We obtained initial ESRD treatment modality from the *rxhist60* file. We used US Census Bureau data to obtain socioeconomic factors at the residential ZIP code level, as a proxy for patient-level socioeconomic status. We used year 2000 Decennial Census data, and American Community Survey (ACS) 5-year data (2007-2011), respectively, for patients starting dialysis prior to or after 2006.[72,73] We obtained outcome data for non-fatal cardiovascular events from linked Medicare Institutional (Part A) and Physician/Supplier (Part B) files. We obtained mortality data (date and cause of death) from the *patient* file: these data are derived from Death Notification forms (CMS-2746) submitted by nephrologists when a patient receiving ESRD treatment dies.

Strengths of the data source:

- Near complete capture of all patients receiving renal replacement therapies (haemodialysis, peritoneal dialysis, or kidney transplantation) at the U.S. population level
- Comprehensive data collection for all patients within 45 days of registry enrolment, including demographics, comorbidities, dialysis modality and access, and key laboratory parameters.
- Linkage to transplant and death registries, as well as Medicare insurance claims data, enabling the study of long-term, clinically relevant, endpoints

Limitations of the data source:

- Causes of kidney failure submitted to the USRDS are not necessarily confirmed by kidney biopsy, so misclassification is inevitable. A previous study measured agreement between biopsy-based

diagnoses and USRDS-derived diagnoses among 227 patients with biopsy-proven GN.[21] Poor overall agreement was largely explained by a large number of "missing" (57%) and "GN not histologically examined" (9%) diagnoses in the USRDS; however, positive predictive values exceeded 90% once a specific GN subtype was selected.

- Comprehensive, time-updated, medication and laboratory data are lacking

2.3. Statistical methods

A number of statistical methods were applied to address the specific aims of this thesis. Additionally, through performing these analyses, I expanded my repertoire of analytic approaches.

2.3.1. Geographic variation and temporal trends in glomerular disease frequency distributions: considering contributions from race-ethnicity to observed findings

When analysing data from the IKBS, I learned how to analyse group- rather than individual- level data, by weighting analyses according to case numbers at each centre. When comparing multiple glomerular disease diagnoses across demographic groups, I also learned the importance of p-value correction for multiple testing, to minimise the risk of a Type 1 error. Most importantly, I focused my analyses on unravelling the influence of geographic region (representing societal, environmental, socioeconomic, or health system factors) from race-ethnicity (representing genetic factors), by comparing differences in frequency distributions across continents both overall and within individual racial-ethnic groups.

When analysing data from the GDCN, p-values were also corrected for multiple testing, while p-values for trend were employed to assess temporal trends. Additional statistical approaches (ANOVA and Kruskall-Wallis testing), were used to compare frequencies across demographic groups. As for the IKBS, a major goal of this study was to determine whether significant associations between glomerular disease subtype and era, identified in the full cohort, held true within demographic sub-groups. Accordingly multiple sub-group analyses and plots were created, which will serve as useful resources to clinicians who are considering differential diagnoses based on patient demographics.

2.3.2. Associations between glomerular disease subtype and clinical outcomes in patients with end-stage kidney failure: considering the influence of confounding

The manuscripts presented in **Chapters 5 and 6** of this thesis, using data from the USRDS, employed more advanced statistical techniques than in the prior two papers. These include the creation of cumulative survival and cumulative incidence plots, use of sequential multivariable Cox regression models to account for groups of confounders (demographics, socioeconomic factors, and clinical characteristics), use of proportional hazard models with calculation of sub-distribution hazard ratios to account for competing events, and use of multiple imputation to handle missing data. In both these manuscripts, we present both unadjusted event rates as well as unadjusted and adjusted hazard ratios, so that researchers, clinicians, and their patients can better understand the expected likelihood of the events of interest once a patients starts dialysis, how these risks compare across glomerular disease subtypes, as well as potential explanations (i.e. confounding influences) for these findings.

Chapter 3. Glomerular disease frequencies by race, sex and region: results from the International Kidney Biopsy Survey

Authors:

Michelle M. O'Shaughnessy, MB BCh MS[1,2], Susan L. Hogan, PhD[2], Bawana D. Thompson, BS CRC[3], Rosanna Coppo, MD[4], Agnes B. Fogo, MD[5], J. Charles Jennette, MD[3]

Affiliations:

[1]Division of Nephrology, Stanford University School of Medicine, Palo Alto

[2]Division of Nephrology and Hypertension, Department of Medicine and the Kidney Centre, University of North Carolina School of Medicine, Chapel Hill

[3]Division of Nephropathology, Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill

[4]Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy

[5]Department of Pathology, Microbiology and Immunology, Division of Renal Pathology, Vanderbilt University Medical Center, Nashville

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3.1. Abstract

Background: Large-scale studies comparing glomerular disease frequencies across continents are lacking.

Methods: We surveyed 29 nephropathology laboratories in 4 continents using a standardized data collection form. We obtained recent consecutive kidney biopsy diagnosis frequencies at each centre and summary demographics for each diagnosis. This report focuses on glomerular disease frequencies by region and race/ethnicity.

Results: Among 42,603 glomerular disease diagnoses reported (median age 47 years, 52% male, 57% white), from a total of 60,340 diagnoses, glomerular disease subtype frequencies differed considerably by continent. Diabetic glomerulosclerosis (19.1%) and focal segmental glomerulosclerosis (FSGS, 19.1%) predominated in North America; lupus nephritis (38.1%) and FSGS (15.8%) predominated in Latin America; IgA nephropathy (22.1%) and focal segmental glomerulosclerosis (FSGS) (14.9%) predominated in Europe; and IgA nephropathy (39.5%) and lupus nephritis (16.8%) predominated in Asia. After stratifying by race, diabetic glomerulosclerosis (17.4% *vs.* 4.3%, p<0.001) and FSGS (17.3% *vs.* 11.8%, p<0.001) were more, and lupus nephritis less (15.8% *vs.* 45.6%, p<0.001), frequent among Latinos in North *vs.* Latin America; FSGS was more (13.1% *vs.* 7.1%, p<0.001), and IgA nephropathy less (27.4% *vs.* 40.5%, p<0.001), frequent among Asians in North America *vs.* Asia; and FSGS (18.9% *vs*. 13.5%, p<0.001) and diabetic glomerulosclerosis (18.7% *vs*. 6.5%, p<0.001) were more, and IgA nephropathy (14.4% *vs.* 25.4%, p<0.001) less, frequent among whites in North America *vs.* Europe.

Conclusions: We determined that glomerular disease frequencies differed by continent, even among patients of similar race/ethnicity. Regional environmental and lifestyle factors, and local biopsy policies, might influence glomerular disease epidemiology independently from race/ethnicity.

3.2. Introduction

Glomerular disease development involves a complex interplay of genetic, epigenetic, and environmental factors,[41,49,74] although the relative contributions from individual exposures to observed demographic and geographic disease distributions remain poorly understood and probably differ by glomerular disease subtype. Prior efforts to systematically compare kidney biopsy data from several countries and regions have been complicated by non-standardized approaches to disease definitions and groupings.[14,39] Whether glomerular disease frequency distributions shift in response to environmental or behavioural changes when individuals move away from their country of ancestral origin to a new region has also not adequately been explored, yet may offer clues to disease pathogenesis.

Determining contemporary glomerular disease diagnosis frequencies among patients who undergo renal biopsy, stratified by race and geographic region, while applying standardized disease nomenclature systems, might greatly assist the planning of future glomerular disease research, by providing realistic estimates of the number of biopsies requiring performance or review in order to detect a threshold number of cases. Additionally, exploring the distributions of specific glomerular disease subtypes across racial groups and geographic regions might uncover new insights into the relative importance of genetic and environmental influences on glomerular disease epidemiology.

We conducted a survey of twenty-nine nephropathology laboratories (including two kidney biopsy registries) throughout the USA, Canada, Europe, Asia, and Latin America. We collected the total number of diagnoses and summary patient demographics for all consecutive and recent (range 1-6 years) kidney biopsy diagnoses identified at each centre. In this report, we specifically focus on glomerular disease diagnoses, comparing disease distributions across geographic regions and patient demographic groups.

3.3. Materials and methods

Patient population and data source:

The International Kidney Biopsy Survey (IKBS) was designed by JCJ and ABF, with support from the American Society of Nephrology Glomerular Diseases Advisory Group (ASN GDAG), the Renal Pathology Society (RPS), and the European Renal Association—European Dialysis and Transplantation Association (ERA-EDTA) Immunonephrology Working Group. Centres were invited to participate in the survey between 2012 and 2013. According to survey instructions (**Supplemental Materials, Appendix A),** all consecutive native kidney biopsy diagnoses reported by the participating centre over a self-selected

recent time period of at least one year were required to be reported. Diagnoses were determined based on light, immunofluorescence, and electron microscopic findings, as available, interpreted in the context of provided clinical data. These data could be gathered prospectively or retrospectively. If two or more diagnoses were identified from a single biopsy specimen, each diagnosis was regarded as a separate observation. Centres were instructed to report demographic data, if available, as summary values for each diagnosis, including: mean age, minimum age, maximum age, number of males, number of females, and number of patients with each of 4 mutually exclusive race/ethnicity categories (white, black, Asian, or Latino), for each diagnosis. If sex or race sub-totals summed to less than the total number of cases for that diagnosis, or if demographic (sex, race, or age) data were missing, the deficit was designated as "missing or unknown" when collating and analysing data.

Exposures and outcomes:

Geographic region [North America (USA or Canada), Latin America, Asia, Europe] was our primary exposure. Race, sex, and mean age were our secondary exposures. Glomerular disease frequency distributions were our primary outcome.

Statistical analysis:

Categorical data (region, race, sex) were summarized as frequencies and percentages and compared across groups using cross tabulation. The median and range for reported mean, minimum, and maximum age values for each diagnosis, weighted by diagnosis frequencies at the individual centres, are reported for each region. Chi-square or Fisher's exact testing, as appropriate, were used to compare the frequencies of each glomerular disease diagnosis across groups. A Bonferroni-corrected 2-sided p-value of <0.004 (0.05/12, to account for multiple comparisons) was considered statistically significant. All data were analysed using SAS Enterprise Guide version 6.1 (Cary, North Carolina). A waiver from Institutional Review Board (IRB) approval was obtained for this study at the coordinating centre (University of North Carolina, Chapel Hill), and individual participating centres obtained local IRB approval on an as needed basis. All submitted data were de-identified and are presented in an aggregate manner.

3.4. Results

Patient population:

Twenty-nine centres participated, including 13 in Europe [Austria, Czech Republic, France, Greece, Italy (n=2), the Netherlands, Norway, Poland (n=2), Russia, United Kingdom (n=2)], 10 in North America (7 in the USA, 3 in Canada), 3 in Latin America (Brazil, Colombia, Mexico), 2 in Asia (Japan, Thailand), and one in Saudi Arabia. For the purposes of this analysis, the centre from Saudi Arabia was included with the 13 European centres. After excluding inadequate specimens and non-specific diagnoses, a total of 60,340 specific native kidney biopsy diagnoses—including 42,603 glomerular disease diagnoses—were reported, over a median of 4 (range 1 to 8) years, and with a median of 428 (range 81-5400) diagnoses annually per centre.

The median of the reported mean ages of patients with a glomerular disease diagnosis was 47.3 (IQR 39.7-56.9) years. Among those where a specific sex was indicated, (n=39,841, 94%), 53% were male. Among those with known race (n=21,829, 51%), 57% were white, 19% were black, 14% were Latino, and 10% were Asian. Population demographics by geographic region are summarized in **Table 1,** and complete demographic data for all diagnoses (including non-glomerular disease diagnoses) are provided by geographic region in **Supplemental Materials, Appendix B**. Patients were youngest at the time of biopsy in Latin America (median of mean ages 30 years, vs. 43-49 years in the other regions), and the proportion of females was also highest in this region (64%, vs. 51-58%). All patients with known race in Asia were Asian, whereas 98% in Europe were white and 97% in Latin America were Latino. Racial composition was more heterogeneous in the USA (54% white, 31% black, 11% Latino, and 4% Asian).

Glomerular disease subtype frequency distributions by region:

Glomerular disease subtype frequencies are summarized by geographic region in **Table 2 and Figure 1.** Focal segmental glomerulosclerosis (FSGS) and diabetic glomerulosclerosis (GS) predominated in the USA (each comprising 19% of all glomerular diagnoses), followed by IgA nephropathy (12%), membranous nephropathy (12%), and lupus nephritis (10%). FSGS was also common in Latin America (16%), although lupus nephritis strongly predominated in this region (38%), while diabetic GS (4%) and IgA nephropathy (6%) were comparatively rare. In contrast, IgA nephropathy predominated in Europe (22%), where the second most frequent diagnosis was FSGS (15%), and especially in Asia (40%), where the second most frequent diagnosis was lupus nephritis (17%).

Glomerular disease subtype frequency distributions by race and region:

Comparing the frequencies of the more common glomerular disease subtypes across regions among patients with a similar reported race revealed some significant shifts in relative disease frequencies

when comparing patients living in North America (USA or Canada) to those living in their region of ancestral origin, **Figure 2**. Comparing Asians in North America to those in Asia, the frequencies of IgA nephropathy (27% vs. 40%, p<0.001), lupus nephritis (13% vs. 17%, p=0.03) were significantly lower, whereas those of FSGS (13% vs. 7%, p<0.001), minimal change disease (6% vs. 3%, p=0.0028), and membranoproliferative glomerulonephritis (MPGN) (2% vs. 1%, p=0.01) were significantly higher. Comparing Latinos in North America to those in Latin America, the frequency of lupus nephritis (15% vs. 45%, p<0.001) was significantly lower, whereas those of FSGS (17% vs. 11%, p<0.001), membranous nephropathy (12% vs. 8%, p=0.0008), IgA nephropathy (13% vs. 6%, p<0.001), and especially diabetic nephropathy (17% vs. 4%, p<0.001) were significantly higher. Finally, comparing whites in North America to those in Europe, significant differences were identified in the frequencies of all common glomerular disease subtypes, except lupus nephritis, with the most notable differences being lower frequencies of IgA nephropathy (14% vs. 25%, p<0.001), pauci-immune glomerulonephritis (GN) (6% vs. 9%, p<0.001), or renal amyloid (2% vs. 5%, p<0.001) and higher frequencies of FSGS (18% vs. 13%, p<0.001), diabetic GS (18% vs. 6%, p<0.001) and thin basement membrane nephropathy (3% vs. 1%, p<0.001).

Glomerular disease subtype distributions by sex

A marked female preponderance was noted for lupus nephritis and thin basement membrane nephropathy, whereas a modest male predominance was noted for acute post-infectious GN, idiopathic nodular glomerulosclerosis (GS), and IgA nephropathy (**Figure 3**). Comparing glomerular disease subtype frequency distributions across sexes (**Supplemental Figure 1**) identified a high frequency of FSGS (19% in males and 15% in females) and diabetic GS (16% in males and 12% in females) in either sex; however, IgA nephropathy was the most frequent diagnosis in males (20%) and lupus nephritis the most frequent in females (20%), overall.

3.5. Discussion

This reports highlights important findings from an international collaborative effort across 29 major nephropathology centres to develop a standardized approach to kidney biopsy disease classification and reporting. In this study focusing on 42,603 glomerular disease diagnoses, among a total of 60,340 specific diagnoses within 58 disease categories, we identified substantial variation in the relative frequencies of glomerular disease diagnoses across the 4 geographic regions examined. Whereas FSGS predominated in North America (USA and Canada), it was the 2nd most common diagnosis in Europe or Latin America, and the 5th most common in Asia. Conversely, while IgA nephropathy predominated in

Europe and Asia, and lupus nephritis in Latin America, these were notably less frequent (3rd and 5th most common, respectively) in North America. In an effort to distinguish the influence of race/ethnicity (i.e. genetic factors) from that of region (i.e. environmental or lifestyle factors, including biopsy policies), we also compared frequency distributions across regions stratified by race/ethnicity. Using this approach, we identified a significantly higher frequency of FSGS, and a numerically higher frequency of diabetic GS, along with significantly lower frequencies of IgA nephropathy and lupus nephritis, among Asians in North America compared to those in Asia. Similarly, the frequency of diabetic GS was dramatically higher, whereas that of lupus nephritis was substantially lower, among Latinos in North America compared to those in Latin America. Finally, FSGS and diabetic GS were significantly more frequent, and IgA nephropathy significantly less frequent, among whites in North America compared to Europe.

The reasons for the generally higher frequencies of diabetic GS and FSGS among biopsied patients in North America, even when compared to patients of a similar racial/ethnic background residing in their country of ancestral origin, cannot directly be determined from this study. Without knowing the size of the referral population (denominator), we could not distinguish whether this finding represents a higher absolute frequency of FSGS or diabetic GS, a lower absolute frequency of comparator diagnoses (e.g. IgA nephropathy or lupus nephritis), a lower threshold to biopsy patients with morbidities such as diabetes or obesity, or a combination of these factors, within North America as compared to in other regions. Given that diabetic GS and obesity-related secondary forms of FSGS are heavily influenced by lifestyle factors, and that the incidences of diabetes and obesity are steadily rising in the USA,[75,76] we suspect that an absolute increase in the biopsy frequencies of diabetic GS and FSGS (as opposed to a major reduction in the incidences of other subtypes) when patients migrate to North America is the most important contributor to this finding. Of additional note, the biopsy term “FSGS” could also include secondary types of FSGS lesions in this category in this survey. Based on the limitations of our data, the question remains as to whether this represents a truly higher disease incidence or a differing biopsy practice. It is possible, for example, that physicians in North America have the lowest threshold to biopsy diabetic or obese patients with modest proteinuria, thus increasing the detection rate for diabetic GS or secondary forms of FSGS, respectively. At the same time, physicians in Asia might be most likely to biopsy patients with isolated haematuria (on account of national urinary screening programs), contributing to the high frequencies of IgA nephropathy and thin basement membrane lesions observed in this region.

Ultimately, additional studies are required to address these hypotheses; however, if FSGS and diabetic GS truly are more frequent in North America, and become more frequent after moving to North America among those immigrating from other regions (representing a waning of the "healthy immigrant effect"[77,78]), then this finding is of major public health relevance. Diabetic nephropathy is the leading cause of end stage kidney disease in the USA, and FSGS is the leading cause among primary glomerular diseases.[79] While cardiovascular risks are generally increased among all patients with chronic kidney disease, they may be particularly so among patients with either of these glomerular disease subtypes.[80,81] Finally, diabetic GS and secondary forms of FSGS are potentially preventable, through promoting healthy lifestyle choices and reducing obesity, issues that are at the forefront of public health campaigns.

Our findings of differing frequencies of certain autoimmune glomerular diseases across regions, particularly a high frequency of lupus nephritis in Latin America and high frequencies of IgA nephropathy in Europe or Asia, also deserve further mention. While these differences may relate to ancestrally-determined genetic factors, as have previously been described,[43,82] our findings support an additional role for environmental factors in disease aetiology i.e. disease predispositions appear to wane when individuals move from their region of ancestral origin to the USA or Canada. Again, whether this finding is explained by differences in lifestyle or environmental exposure factors, by differences in biopsy practices (e.g. approach to investigating isolated haematuria, or approach to repeat biopsies in patients with lupus), and/or by a relative increase in FSGS or diabetic GS risk that outweighs the risk for auto-immune disease development, should be the subject of future studies.

In addition to examining differences in glomerular disease frequency distributions by race and region of residence, we also explored differences in glomerular disease frequencies by patient sex. Although many of our findings have previously been reported (e.g. a predominance of lupus nephritis among females, and of IgA nephropathy among males), by reporting frequency distributions of glomerular disease within males and females separately, we provide a useful summary of the overall disease burden within these patient groups. Also, while we confirmed that lupus nephritis was the most common glomerular disease among females, and IgA nephropathy the most common among males, neither sex was spared from the high prevalence of FSGS and diabetic GS that we identified in the cohort overall.

Our findings generally support, and supplement, those reported from single centres or regional databases from the continents examined. For example, multiple studies in the USA have reported that FSGS is the most frequent glomerular disease diagnosis among biopsied populations,[29,31,33,37,58,60,63,64,83]

although only one recent study has described the escalating frequency of diabetic nephropathy in the USA.[83] In Europe, IgA nephropathy is reported to be the most frequent glomerular disease diagnosis in Lithuania,[84] Northern Ireland,[54] Croatia,[85] Poland,[86] the Czech republic,[36,53] Spain,[50] and Italy.[51,87] However, membranous nephropathy was recently reported to be most frequent glomerular disease in biopsies at a centre in Turkey,[88] non-IgA mesangioproliferative GN at a centre in Serbia,[89] and mesangioproliferative GN with or without IgA deposition (in the most recently reported era) at centres in Germany[90] and Romania.[91] In Asia, IgA nephropathy is consistently the most frequently observed glomerular disease in studies from Korea[35,55] and China,[56,92] corroborating our data from Japan and Thailand. Finally, FSGS and lupus nephritis are generally reported to be the most frequent primary and secondary glomerular disease subtypes, respectively, in Latin America, although which of these two is the most frequent overall varies by study.[34,59,93,94] These consistencies between our and prior reports validate our study findings, and add credibility to our data regarding the relative frequencies of less common glomerular disease subtypes (for which existing data are less consistent), and our findings regarding discrepant disease frequencies in individuals of a similar race/ethnicity living in different regions (which, to our knowledge, has not previously been examined).

Our study does have several limitations. As data were most commonly obtained retrospectively within each of the centres, misclassification may have arisen when converting diagnoses from non-standardized original diagnoses to the standardized diagnosis categories adopted for the study. Information regarding biopsy management and processing procedures (e.g. number of sections examined, routine use of immunofluorescence and/or electron microscopy techniques) was not collected, and the potential confounding influence of such factors on study findings could not be evaluated. Data were provided at the diagnosis level and not the patient level to avoid patient identification; thus, diagnoses of additional primary diseases (e.g. primary FSGS in addition to IgA nephropathy or diabetic GS) versus secondary lesions (e.g. secondary segmental sclerosis in the setting of IgA nephropathy or diabetic GS) could not be distinguished, which may be particularly relevant for FSGS and diabetic GS diagnoses. While we obtained data from 29 centres in 17 countries and across 4 continents, it remains unlikely that the disease burden we report is perfectly representative of the worldwide disease burden. In particular, the number of centres surveyed in Asia and Latin America was relatively small, and patients residing in North America who were reported to be of Asian or Latino race/ethnicity might have originated from countries other than those included (e.g. China, India, Argentina, or Chile). Centres in Africa, Australia, and parts of Europe (especially Eastern Europe) were not represented. Some of the included centres may have been specialty referral centres for certain

glomerular disease subtypes, inflating local disease frequencies at that centre, albeit that this effect should be diluted by inclusion of more than one centre per region. Demographic data, especially race/ethnicity, were frequently missing, and differentially so across regions. However, centres generally either provided or did not provide these data, and did so uniformly across all glomerular disease diagnoses; thus, while missing data reduced our sample size (by reducing the numbers of centres included in certain demographic analyses), when examining particular sex or racial/ethnic groups we expect our conclusions regarding glomerular disease frequency distributions across demographic groups to be valid. Without individual patient level data regarding age, we could not stratify by age group in our analyses; thus, we could not evaluate whether differences in biopsy practices or disease incidences in certain age groups might have contributed to our study findings, and would welcome this as a focus of future studies. Finally, an estimate of referral population size was available only from two of the centres, and thus background biopsy rates for each of the regions could not be calculated.

Despite these limitations, our study has several strengths. In addition to identifying marked differences in glomerular disease epidemiology across geographic regions, and providing data to suggest that environmental/lifestyle factors and biopsy policies might contribute importantly to this finding, this study marks the first step toward creating a collaborative, international, glomerular disease registry. The potential to expand these efforts to additional centres, and to collect patient-level clinical data along with electronic histologic images, is exciting. In the meantime, the data collected for this project can be meaningfully applied to future research, by providing estimates of disease burden within particular regions or demographic groups, thus guiding disease or high-risk patient identification strategies, and informing hypothesis-driven studies aiming to explain these epidemiologic findings.

To conclude, in this first ever International Kidney Biopsy Survey (IKBS) involving participation from 29 centres across 4 continents, we identified marked variations in glomerular disease frequencies across geographic regions, even within specific racial/ethnic groups, with a particularly high frequency of FSGS and diabetic GS identified among patients in the USA. Whether these findings reflect differences in patient behaviours (e.g. dietary intake, weight management), environmental exposures (e.g. infections, pollutants), and/or biopsy practices (e.g. urinary screening programs, threshold to biopsy patients with diabetes), should be the subject of future studies. Additionally, we confirmed that sex predispositions to glomerular disease development previously described in smaller, often single-centre, patient populations, are also evident when examining data from over 40,000 diagnoses. This study represents an exciting step toward studying glomerular disease at the global level, and demonstrates the feasibility

of engaging multiple stakeholders from diverse geographic, economic, and cultural regions in a collaborative research effort.

3.6. Tables and Figures (subsequent pages)

Table 1: Demographic characteristics among 29 international centres surveyed, by geographic region (n=42,603 glomerular disease diagnoses).

Characteristic	USA/Canada (10 centres) n=23,391	Europe (14 centres) n=15,042	Asia (2 centres) n=1,609	Latin America (3 centres) n=2,561
Age variables (median, range*)				
Min	1 (0.1-37)	2 (0.3-34)	15 (13-78)	8 (1-64)
Mean	49 (27-66)	48 (25-63)	43 (29-82)	30 (17-71)
Max	90 (71-100)	89 (57-101)	88 (29-94)	81 (17-84)
Male sex, n (% of non-missing)[#]	12,004 (52.3)	7169 (56.4)	797 (49.5)	930 (36.4)
Missing sex, n (% of total)	439 (1.9)	2320 (15.4)	0	3 (0.1)
Race, n (% of non-missing)[#]				
White	7231 (54.2)	5118 (98.2)	0	14 (0.8)
Black	4179 (31.4)	44 (0.8)	0	36 (2.1)
Asian	482 (3.6)	40 (0.8)	1569 (100)	0
Latino	1440 (10.8)	8 (0.2)	0	1668 (97.1)
Missing race, n (% of total)	10,059 (43.0)	9832 (65.4)	40 (2.5)	843 (32.9)

*Individual patient-level age data not available. Instead, values represent the weighted median and range, by region, for each diagnosis-level age variable (mean, minimum, and maximum age) [#]Chi-square $p<0.05$.

Table 2: Glomerular disease diagnosis frequencies among 29 international centres surveyed, by geographic region (n=41,527 glomerular disease diagnoses).

Glomerular disease subtype	USA/Canada (10 centres) n=23,391		Europe (14 centres) n=15,042		Asia (2 centres) n=1,609		Latin America (3 centres) n=2,561	
	n	%	n	%	n	%	n	%
FSGS[#]	4462	19.1	2238	14.9	111	6.9	404	15.8
IgAN/HSP[#]	2762	11.8	3318	22.1	636	39.5	156	6.1
Diabetic GS[#]	4460	19.1	1049	7.0	172	10.7	110	4.3
Membranous nephropathy[^]	2710	11.6	1885	12.5	162	10.1	284	11.1
Lupus GN[#]	2297	9.8	1524	10.1	270	16.8	976	38.1
Pauci-immune GN[#]	1220	5.2	1198	8.0	41	2.6	121	4.7
Minimal change disease[#]	967	4.1	964	6.4	55	3.4	175	6.8
MPGN/C3GP combined[#]	609	2.6	557	3.7	17	1.1	71	2.8
Renal amyloid[#]	509	2.2	661	4.4	14	0.9	37	1.4
TMA[#]	652	2.8	336	2.2	13	0.8	30	1.2
TBMN[#]	520	2.2	218	1.5	50	3.1	19	0.7
MesProlif/Prolif GN NOS[#]	452	1.9	263	1.8	4	0.3	62	2.4
Chronic Sclerosing GN NOS[#]	245	1.1	123	0.8	1	0.1	6	0.2
Acute PIGN[#]	182	0.8	115	0.8	26	1.6	43	1.7
MIDD[#]	249	1.1	81	0.5	6	0.4	4	0.2

Fibrillary GN[#]	291	1.2	39	0.3	2	0.1	2	0.1
*Other glomerular disease[#]	101	0.4	175	1.2	3	0.2	33	1.3
Cryoglobulinaemic GN	155	0.7	112	0.7	13	0.8	5	0.2
Alport's syndrome[#]	182	0.8	61	0.4	9	0.6	8	0.3
Anti-GBM GN (+/-ANCA)	123	0.5	80	0.5	1	0.1	5	0.2
C1q nephropathy[#]	137	0.6	14	0.1	1	0.1	3	0.1
Idiopathic nodular GS[#]	106	0.5	31	0.2	2	0.1	7	0.3

[#] Chi-square p<0.002 ^ Chi-square p=0.0022 *Includes glomerular disease diagnoses with less than 100 cases overall (diffuse mesangial sclerosis, Finnish type congenital nephrotic syndrome, immunotactoid glomerulopathy, collagenofibrotic glomerulopathy, fibronectin glomerulopathy, IgM nephropathy, polyarteritis nodosa, preeclampsia/eclampsia, Fabry disease, lipoprotein glomerulopathy, sickle cell glomerulopathy). FSGS, focal segmental glomerulosclerosis, IgAN, IgA nephropathy; HSP, Henoch Schoenlein purpura; GS, glomerulosclerosis; GN, glomerulonephritis; MPGN, membranoproliferative GN; G3GP, C3 glomerulopathy; TMA, thrombotic microangiopathy; TBMN, thin basement membrane nephropathy; MesProlif, mesangioproliferative; NOS, not otherwise specified; PIGN, post-infectious GN; MIDD, monoclonal immune deposition disease; GBM, glomerular basement membrane; ANCA, anti-neutrophil cytoplasmic antibody.

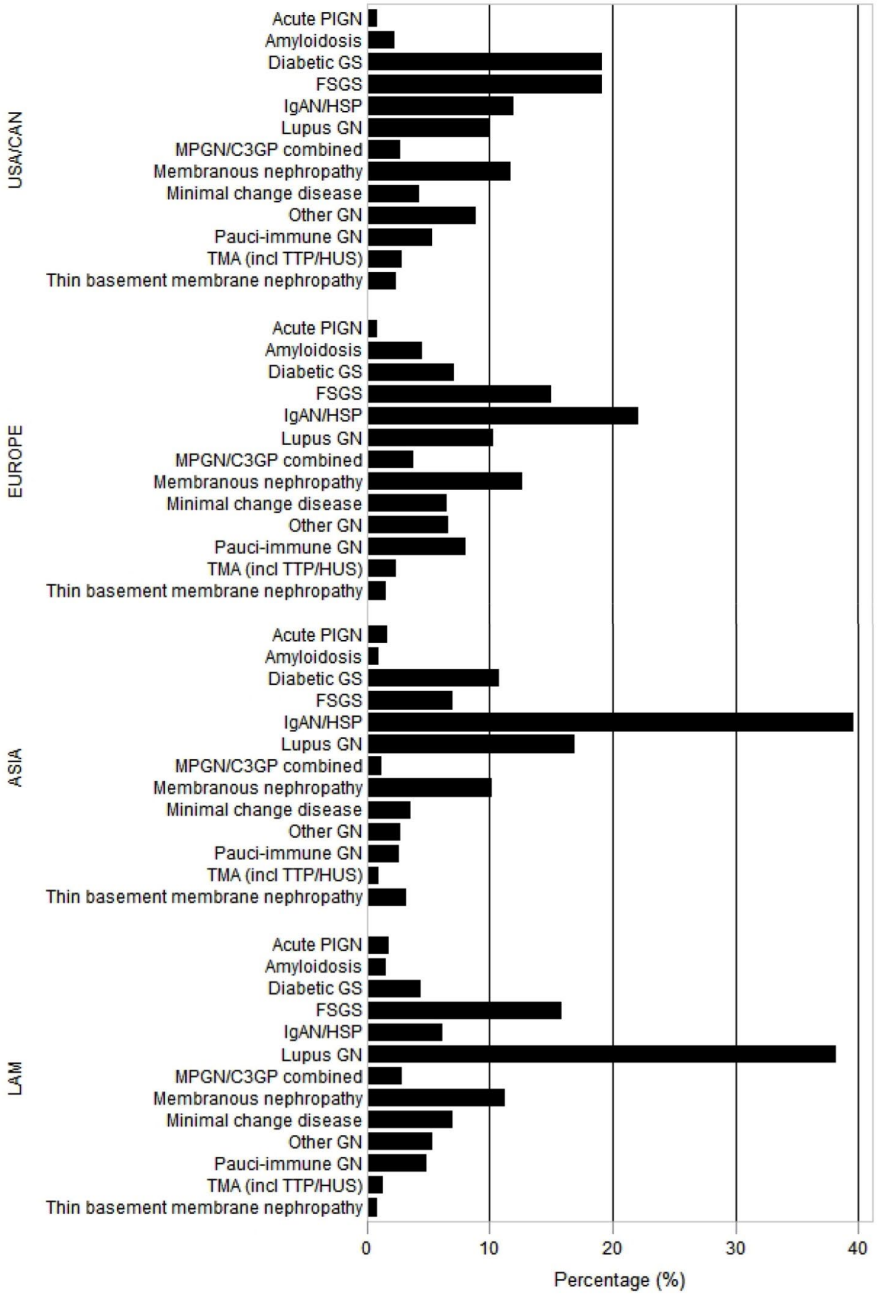

Figure 1. Glomerular Disease Subtype Kidney Biopsy Frequencies, by Geographic Region. Showing the 13 most common glomerular disease diagnoses only. CAN, Canada; LAM, Latin America; PIGN, post-infectious glomerulonephritis; GS, glomerulosclerosis; FSGS, focal segmental glomeruloslcerosis; IgAN, IgA nephropathy; HSP, Henoch Schonlein purpura; GN, glomerulonephritis; MPGN, membranoproliferative GN; C3GP, C3 glomerulopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.

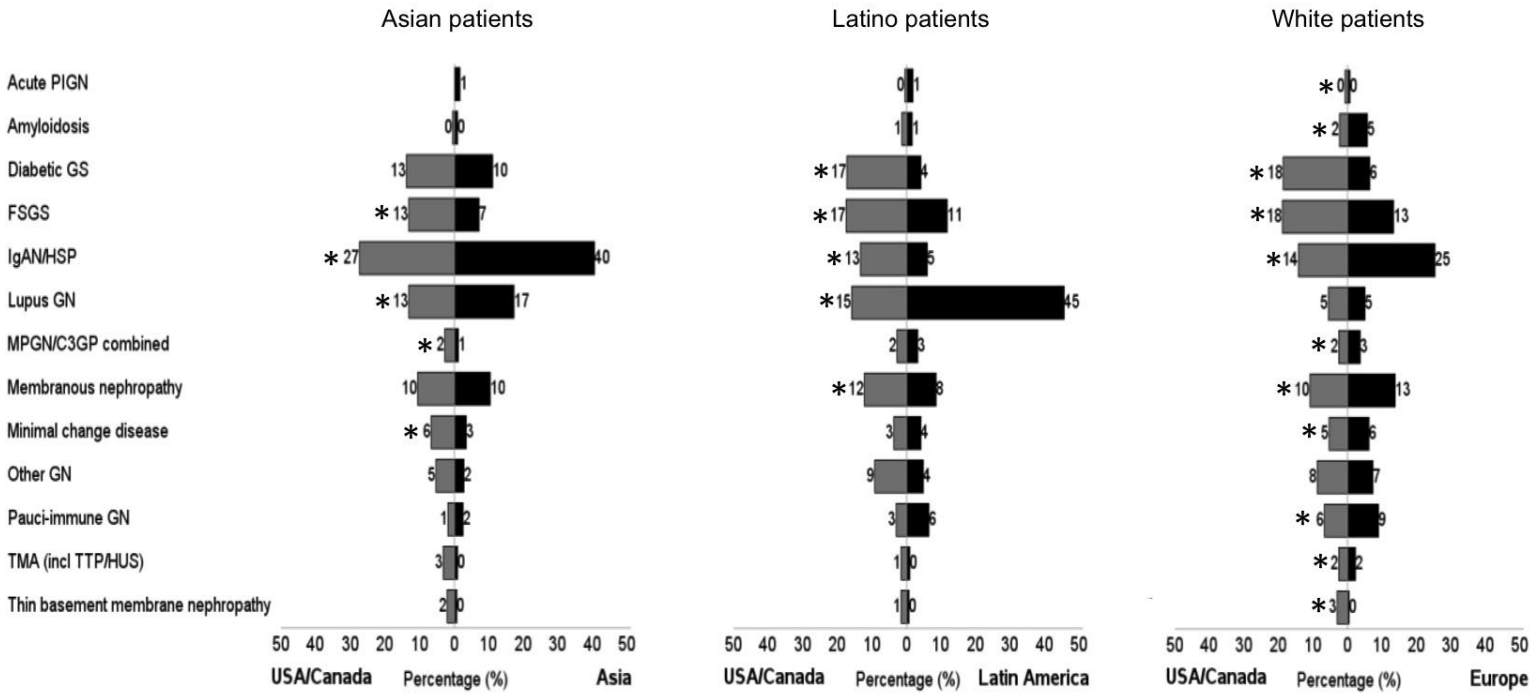

Figure 2, Glomerular Disease Subtype Kidney Biopsy Frequencies, by Race, Comparing Regions of Ancestral Origin to USA/Canada. Showing the 13 most common glomerular disease diagnoses only. * p<0.004. PIGN, post-infectious glomerulonephritis ; GN, glomerulonephritis; GS, glomerulosclerosis; FSGS, focal and segmental glomeruloslcerosis; IgAN, IgA nephropathy; HSP, Henoch Schonlein purpura; GN, glomerulonephritis; MPGN, membranoproliferative GN; C3GP, C3 glomerulopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.

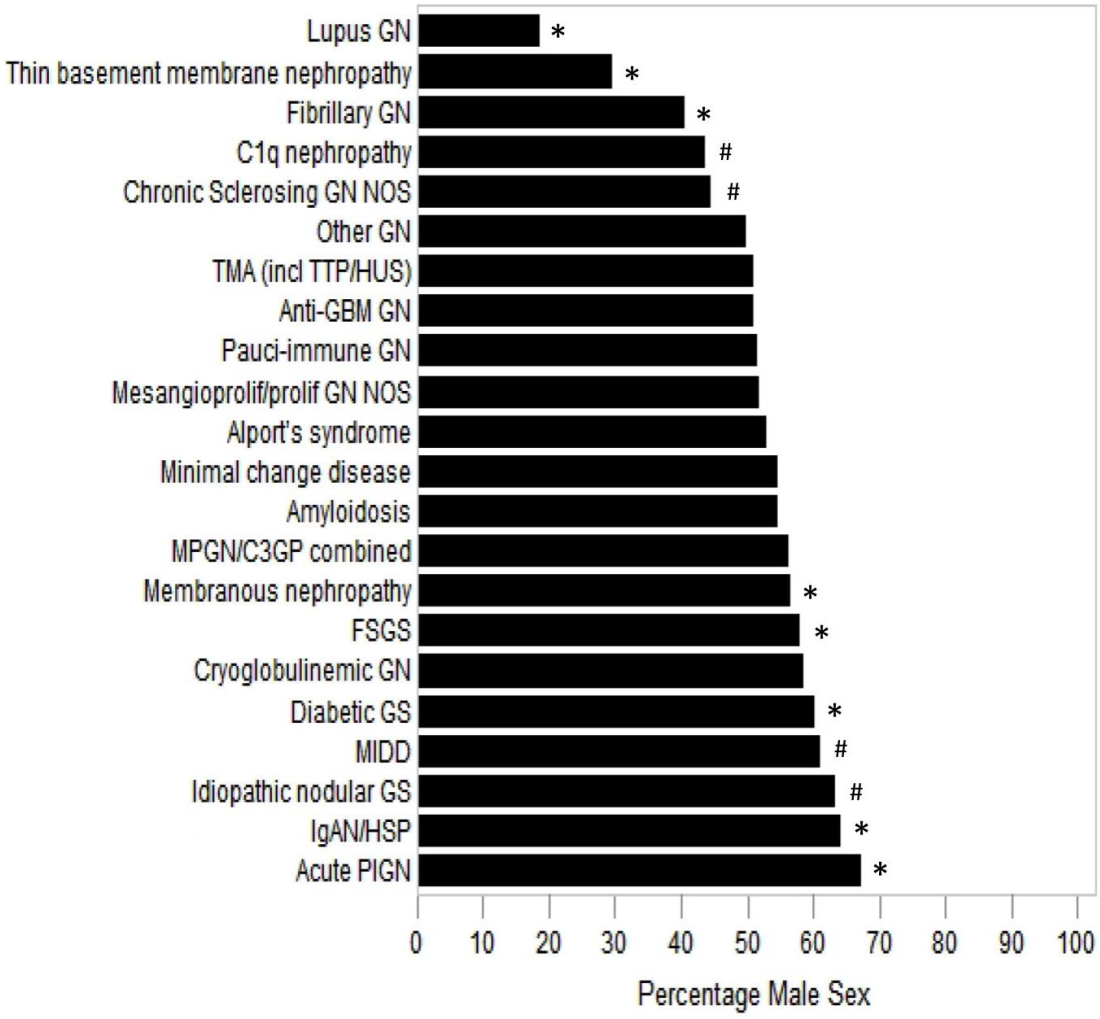

Figure 3. Male Sex Frequencies among Glomerular Disease Subtypes. Remaining patients female (missing sex excluded). *** p<0.002. #0.002<p< 0.05.** GN, glomerulonephritis; NOS, not otherwise specified; TMA, thrombotic microangiopathic anemia; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; GBM, glomerular basement membrane; MPGN, membranoproliferative GN; C3GP, C3 glomerulopathy; FSGS, focal and segmental glomerulosIcerosis; GS, glomerulosclerosis; MIDD, monoclonal immune deposition diseases; IgAN, IgA nephropathy; HSP, Henoch Schonlein purpura; PIGN, post-infectious GN. "Other GN" includes diagnoses with less than 100 cases overall (diffuse mesangial sclerosis, Finnish type congenital nephrotic syndrome, immunotactoid glomerulopathy, collagenofibrotic glomerulopathy, fibronectin glomerulopathy, IgM nephropathy, polyarteritis nodosa, preeclampsia/eclampsia, Fabry disease, lipoprotein glomerulopathy, sickle cell glomerulopathy).

Chapter 4. Temporal and Demographic Trends in Glomerular Disease Epidemiology in the Southeastern United States, 1986-2015

Authors:

Michelle M. O'Shaughnessy, MD, MS[1,2,3]; Susan L. Hogan, PhD, MPH[2]; Caroline J. Poulton, MSW[2]; Ronald J. Falk, MD[1,2]; Harsharan K. Singh, MD[1,2]; Volker Nickeleit, MD[1,2]; J. Charles Jennette, MD[1,2]

Affiliations:

[1]Division of Nephropathology, UNC Department of Pathology and Laboratory Medicine, Chapel Hill

[2]UNC Kidney Center, UNC School of Medicine, Chapel Hill

[3]Division of Nephrology, Stanford University School of Medicine, Palo Alto

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4.1. Abstract

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

Design, setting, participants, and measurements: In this cross-sectional, observational study, we identified all patients with a native kidney biopsy specimen demonstrating one of 18 widely recognized glomerular disease diagnoses referred to the University of North Carolina (UNC) Chapel Hill Division of Nephropathology between 1986 and 2015. Biopsy era (1986-1995, 1996-2005, 2006-2015) and demographics (age, sex, 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, 50.8% male, 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 3 decades (5.5%, 11.4%, and 19.1% of diagnoses, respectively, p for trend <0.001). The frequency of focal segmental glomerulosclerosis 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, ANCA/pauci-immune glomerulonephritis) or declined (minimal change disease, membranous nephropathy, membranoproliferative glomerulonephritis, lupus nephritis). These temporal trends were largely preserved within all demographic sub-groups, 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 3 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 behavioural and environmental exposures that likely underlie these findings should be the focus of future hypothesis-driven research.

4.2. 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 risk for focal segmental glomerulosclerosis (FSGS) in African Americans, or IgA nephropathy in Asians, encouraged the discovery of racially determined genetic risk variants.[26,95] Associations between population sanitation standards or socioeconomic status and risks for certain glomerulonephritis subtypes suggest an etiologic role for environmental and lifestyle factors in disease pathogenesis.[49,45] 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 U.S., prior studies exploring glomerular disease epidemiology identified a marked increase in the frequency of FSGS at the end of the 20th century.[28-30,33,37] Whether this trend continued in to 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 African Americans.[62] Temporal trends are less consistent across studies for other glomerular disease subtypes, explained by differences in population demographics (e.g. Caucasian,[30] military,[63] or urban-dwelling patients[28]) or clinical inclusion criteria (e.g. nephrotic syndrome[28,29] vs. any glomerular disease[30,64]). 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 UNC and to academic and community practices throughout the southeastern U.S. since the 1970's. By examining native kidney biopsy cases submitted between 1986 and 2015, we aimed to describe temporal trends in glomerular disease frequencies over 3 decades and to explore the influence of demographic factors on glomerular disease frequency distributions.

4.3. Materials and Methods

Patient population:

All native kidney biopsy specimens referred to UNC Nephropathology (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 or its neighbouring 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 appeared 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 focal segmental glomerulosclerosis (FSGS),[96] all Ehrenreich and Churg stages of membranous nephropathy,[97] and all International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classes of lupus nephritis[98] were grouped into respective FSGS, membranous nephropathy and lupus nephritis categories. Dense deposit disease (membranoproliferative GN, type 2) was analysed separately from other forms of membranoproliferative glomerulonephritis (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, as the distinction between these two disease entities was only recently recognized.[99] The uncommon C1q and IgM mesangial nephropathies were subsumed in minimal change disease and FSGS categories, based on the light microscopic pattern of injury. A diagnosis of pauci-immune necrotizing and crescentic GN was based on pathologic phenotype without requiring serologic anti-neutrophil cytoplasmic antibody (ANCA) positivity. Anti-glomerular basement membrane (GBM) GN that was also ANCA-positive was included in the anti-GBM GN category.

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

Exposures, outcomes, and covariates:

Temporal era was our primary exposure, categorized in to 3 consecutive 10-year time-intervals (1986-1995, 1996-2005, 2006-2015) for tabular presentation and data analysis, and 6 consecutive 5-year time-intervals (1986-1990, 1991-1995, 1996-2000, 2001-2005, 2006-2010, 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 sub-groups, as well as by typical mode of clinical presentation for a given subtype (nephrotic vs. nephritic syndrome[100]). 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 analysis:

Categorical variables were expressed as frequencies (percentages) and compared using chi-square testing, or Fisher's exact testing, as appropriate. When analysing differences across study eras, p-for-trend values are reported. Continuous variables were expressed as means (standard deviations), 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 (Cary, NC). A two-sided p-value of less than 0.05 was considered statistically significant when analysing demographic data and a Bonferroni correction for multiple comparisons (0.05/18= 0.0027) was applied when analysing trends across 18 glomerular disease subtypes.

Institutional Review Board (IRB) approval for the study was obtained from the UNC Biomedical IRB (Study #97-0523).

4.4. Results

Patient population:

38,472 kidney biopsies (33,391 native and 5,081 transplant) were evaluated between 1986 and 2015. Biopsy frequencies increased annually from 390 (1986) to 1,923 (2015). Of these, 22,516 native kidney specimens had one of the 18 study diagnoses. From these, 1,142 repeat biopsies in 1,016 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 (±18.3) years, 50.8% were male, 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±19.1, 46.9±18.2, and 50.4±17.9 years, respectively, $p<0.001$). The largest number of specimens (54.4% of all samples with a documented state of origin) was received from centres in North Carolina, while 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 to those of the population of North Carolina. Male sex in our cohort was similar to that reported for North Carolina in the 2010 Census (51% male),[101] 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% vs. 69%), Latino ethnicity (3% vs. 8%), and Asian race (1% vs. 2%) were less prevalent. In both populations, Asian race and Latino ethnicity increased over time, while white race declined and black race remained stable.

Temporal trends in glomerular disease frequency:

Renal biopsy frequencies, by study era and glomerular disease subtype, are provided in Table 2 and Figure 1. In the earliest era (1986-1995), FSGS predominated (22.6% of studied cases), 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 membranous nephropathy (13.8%) in the middle, and diabetic glomerulosclerosis (19.1%) in the most recent, era

Significant temporal changes in glomerular disease subtype relative frequencies were observed (Table 2 and Figure 1). Most notable was a steady increase in the frequency of diabetic glomerulosclerosis over the 3 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 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, while 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 immunoglobulin deposition disease frequencies.

Temporal trends in glomerular disease frequencies by age, sex, and race:

Temporal trends in males or females mirrored those in the overall cohort (Supplemental Figure S1). However, differences between sexes were observed at a cross-sectional level. For example, lupus nephritis was more frequent in females than males (20.5% vs. 4.7%), while the opposite was true for IgA nephropathy (7.7% vs. 12.8%). Sex distributions by glomerular disease subtype are shown in Table 3 and Supplemental Figure S2.

For black or white patients, temporal trends were also similar to those observed in the full cohort (Supplemental Figure S1). Comparing races cross-sectionally, however, lupus nephritis (20.9% vs. 6.3%) and FSGS (33.6% vs. 20.4%) were more frequent, and IgAN (2.3% vs. 14.9%) and ANCA/pauci-immune GN (3.3% vs. 11.4%) less frequent, among blacks. Racial distributions, by subtype, are presented in Table 3 and Supplemental Figure S2.

Temporal trends by age-category (children, young-adults, middle-aged adults, older adults) are also presented in Supplemental Figure S1. 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% vs. 27.3%) but rare in older adults (2.2%), while 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) patients were most likely to have minimal change disease, very old (>79 years) 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; IgAN was most frequent in white, male, young adults, whereas lupus nephritis peaked in black, female, young adults, for example.

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 MCD 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.

4.5. Discussion

In this study of 21,374 patients with a biopsy-confirmed glomerular disease diagnosis residing predominantly in the southeastern U.S., we identified significant temporal shifts in the epidemiology of many glomerular disease subtypes over the past 3 decades (1986-2105). Most striking was a marked increase in renal biopsy frequency of diabetic glomerulosclerosis, from 5.5% of cases in the earliest decade to 19.1% of cases 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 U.S. cohorts,[28-30,33,37] 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 sub-groups.

Interpretation of our study is complicated by the steadily increasing biopsy referral rate to UNC over the study interval. While 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: a) a declining threshold to biopsy patients; b) an increase in the referral population size, mirroring that occurring in North Carolina;[102,103] c) increasing numbers of nephrologists referring biopsies to UNC; d) 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 or diabetic glomerulosclerosis) underwent more marked increases in disease frequency than those with a more clearly established genetic or auto-immune 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 cases 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 2-fold between 1995 and 2010.[104]

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 sub-groups. In summary, we did not identify convincing evidence that demographic shifts in our study population were responsible for the changes in glomerular disease frequencies we observed, and suggest that changes in lifestyle/environmental factors, or in clinical practice, are more likely to underlie our findings.

When compared to prior studies exploring glomerular disease epidemiology in the U.S., 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.[30] Second, we included all age-groups unlike studies focusing only on adults.[31,64] 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, in order to capture a wide spectrum of patients undergoing kidney biopsy for evaluation of suspected glomerular disease. This differs from prior studies limited to patients with the nephrotic syndrome,[28,29] proteinuria in excess of 2g/24 hours,[33] or a more restricted set of primary glomerular disease diagnoses.[29,31,37,60] Both of the prior studies that included a wide spectrum of primary and secondary glomerular diseases[30,64] excluded cases with diabetic glomerulosclerosis, prompting our decision to analyse our data with and without diabetic glomerulosclerosis to facilitate comparisons to 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,[31,64] recent reports of U.S. 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[28-30,33,37], particularly among African

Americans, was again seen in our patient cohort. However, our study is the first to demonstrate 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,[62] 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 primary/idiopathic cases, in secondary (e.g. obesity-related) cases, or in 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 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 U.S. over the same time interval.[76] Additionally, an increasing tendency to biopsy older patients or to search for non-diabetic glomerular diseases among diabetic patients,[105,106] might underlie these findings.

Considering other glomerular disease subtypes, the declining frequency of membranous nephropathy we observed was reported by some,[33] but not all,[28-31] prior studies, while a stable frequency of IgA nephropathy[29,30,33] and declining frequency of minimal change disease[28-31] have more consistently been observed. With respect to the declining frequency of minimal change disease, paediatric 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 anti-phospholipase 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[60] and a higher risk for lupus nephritis in younger black or female patients[107]) in a large and contemporary U.S. cohort. We also comprehensively analysed glomerular disease frequencies according to several combinations of demographic factors and typical modes of glomerular disease presentation (nephrotic vs. nephritic), which may serve as useful resources to clinicians evaluating

patients in the clinic, or to 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 or 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 UNC Nephropathology 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, U.S. population that the frequencies of many glomerular disease subtypes have shifted considerably over the past 3 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 we observed, given the adverse outcomes[108] and increased healthcare costs[109] 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 in to disease pathogenesis or therapeutic opportunities.

4.6. Tables and figures (subsequent pages)

Table 1: Temporal trends in patient demographics among the study cohort of patients with specified glomerular disease diagnoses. Percentages (except *missing %s*) represent column percentages among patients with complete data.

	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, % (n					<0.001
0-17 years	**8.3** (265)	**5.3** (417)	**3.3** (334)	**4.8** (1016)	
18-39 years	**32.0** (1020)	**30.6** (2415)	**24.8** (2518)	**28.0** (5953)	
40-64 years	**40.2** (1282)	**44.5** (3515)	**47.0** (4772)	**45.1** (9569)	
>64 years	**19.6** (624)	**19.6** (1547)	**24.9** (2525)	**22.1** (4696)	
Missing age %	*2.0*	*0.8*	*0.1*	*0.7*	
Male sex, % (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*	

Table 2: Temporal trends in the renal biopsy frequencies of glomerular disease subtypes among the study cohort of patients with specified glomerular disease diagnoses. All values represent column % (n).

	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*	**5.5** (179)	**11.4** (903)	**19.1** (1942)	**14.2** (3024)
Membranous nephropathy*	**17.8** (579)	**13.8** (1097)	**10.6** (1078)	**12.9** (2754)
Minimal change disease*	**8.8** (286)	**5.5** (441)	**4.1** (415)	**5.3** (1142)
MPGN*	**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*	**0.6** (20)	**0.6** (51)	**1.6** (160)	**1.1** (231)
Dense deposit disease (DDD)	**0.3** (8)	**0.1** (9)	**0.2** (22)	**0.2** (39)
Fabry disease[&]	**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*	**12.8** (416)	**13.9** (1109)	**11.2** (1142)	**12.5** (2667)
IgAN[#]	**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*	**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[#]	**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)**

*Chi-square test for trend p<0.0027; [#]Chi-square test for trend p <0.05 but >0.0027. [&]Fisher's Exact test p <0.05 but >0.0027. FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN (non-DDD); MIDD, monoclonal immune deposition disease; DDD, dense deposit disease; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; TBM, thin basement membrane; GBM, glomerular basement membrane.

Table 3: Demographic characteristics (sex, race, and age) of patients with each of the 18 studied glomerular disease subtypes. Denominator is number of persons with non-missing data for the variable.

	Male sex, % (n)	Race, % (n)					Age in yrs, mean (SD)
		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)	*	*	**50.8** (19.3)
Amyloidosis	**55.0** (264/480)	**70.3** (286/407)	**27.3** (111/407)	*	*	*	**62.9** (11.1)
MIDD	**58.7** (135/230)	**66.3** (134/202)	**30.7** (62/202)	*	*	*	**61.8** (12.5)
Dense deposit disease (DDD)	**41.0** (16/39)	**70.0** (21/30)	*	*	*	*	**33.1** (20.1)
Fabry disease	**87.5** (14/16)	**84.6** (11/13)	*	*	*	*	**40.8** (14.6)
Collagenofibrotic glomerulopathy	*	*	*	*	*	*	**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)	*	**60.6** (16.8)
TBM lesion	**24.2** (113/467)	**73.3** (274/374)	**21.4** (80/374)	**4.0** (15//374)	*	*	**39.9** (16.1)
Fibrillary GN	**39.6** (114/288)	**82.6** (199/241)	**17.0** (41/241)	*	*	*	**57.0** (11.2)
Anti-GBM nephritis	**51.5** (101/196)	**85.1** (137/161)	**11.2** (18/161)	*	*	*	**53.5** (19.3)
Alport syndrome	**57.1** (60/105)	**76.8** (63/82)	**15.9** (13/82)	*	*	*	**25.6** (13.7)
Immunotactoid GN	**46.2** (12/26)	**61.1** (11/18)	*	*	*	*	**49.7** (16.4)

* Cell contains <10 patients. FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN (non-DDD); MIDD, monoclonal immune deposition disease; DDD, dense deposit disease; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; TBM, thin basement membrane; GBM, glomerular basement membrane.

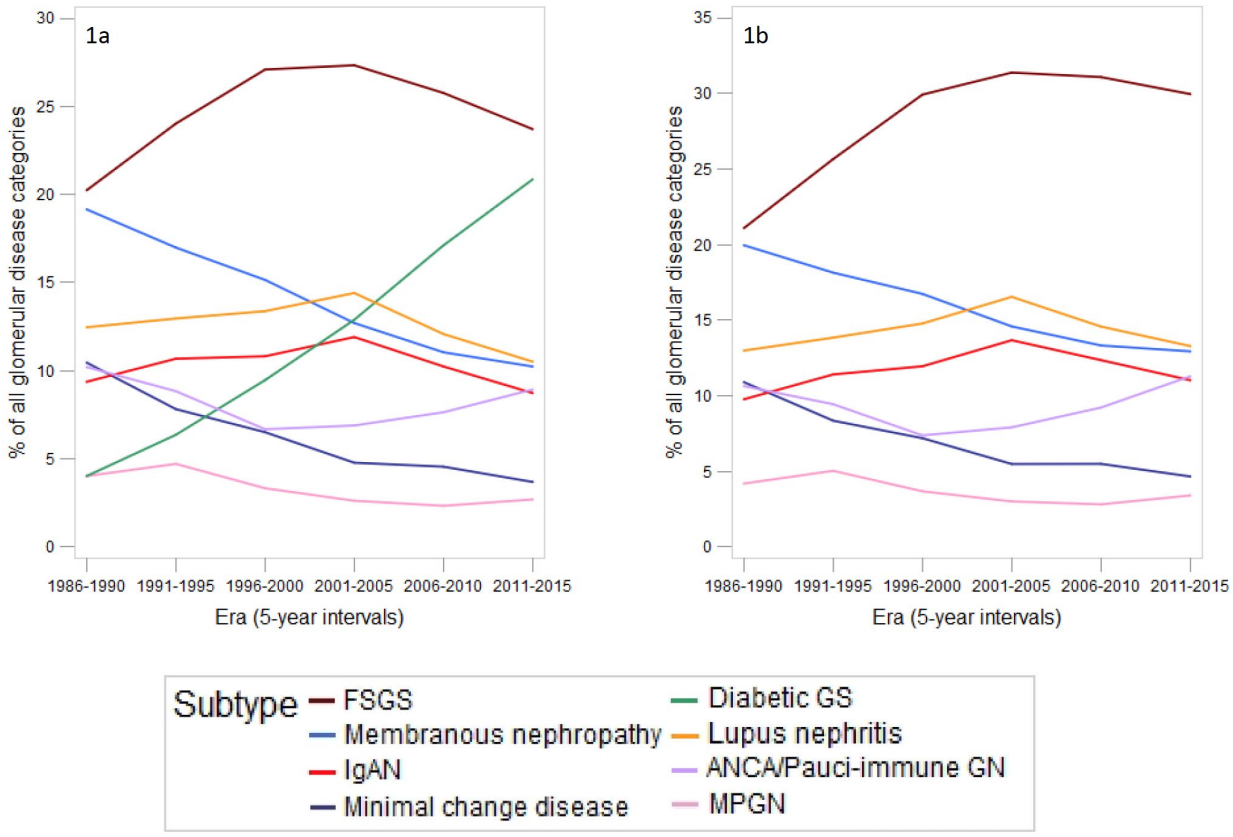

Figure 1: Temporal trends in the relative renal biopsy frequencies of the most common glomerular disease subtypes, 1986-2015. Figure 1a. Frequencies of the 8 most common glomerular disease subtypes shown as a proportion of the entire cohort. Figure **1b.** Frequencies of the 7 most common glomerular disease subtypes shown as a proportion of remaining subtypes after excluding diabetic GS. FSGS, focal segmental glomeruloslcerosis; GS, glomerulosclerosis; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis excluding DDD.

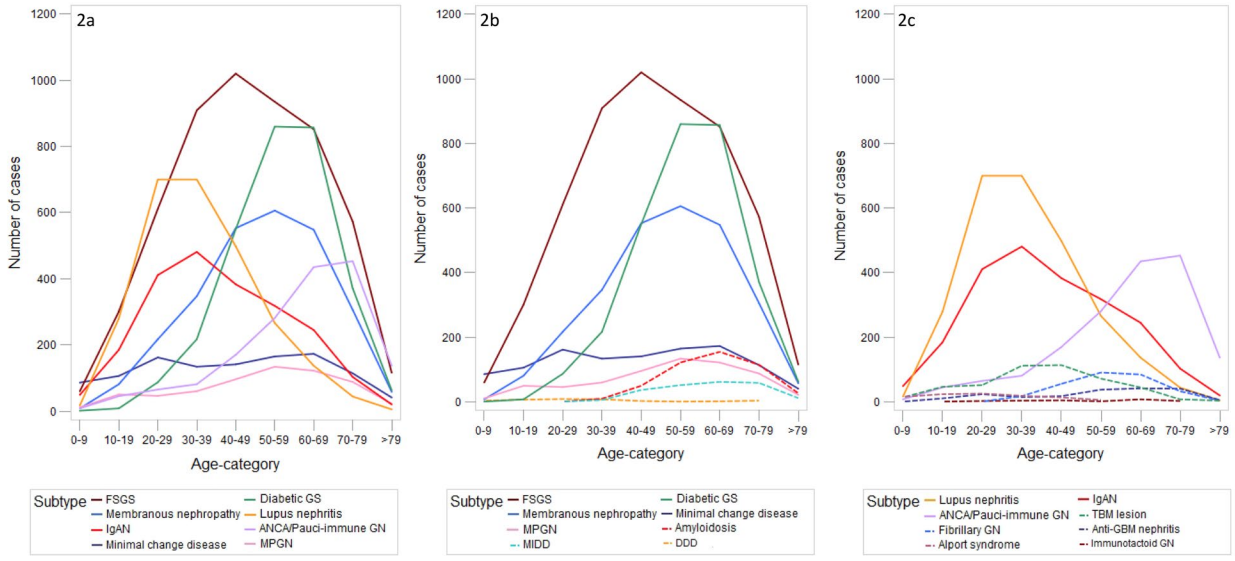

Figure 2. Absolute renal biopsy diagnosis frequencies of the most common glomerular disease subtypes according to patient age category. 2a, all subtypes: number of cases of each of the 8 most common glomerular disease subtypes shown. **2b, nephrotic subtypes:** number of cases of each of the 8 most common glomerular disease subtypes that often present with nephrotic syndrome shown (Fabrys disease and collagenofibrotic glomerulopathy not shown) **2c, nephritic subtypes:** number of cases of each of the 8 glomerular disease subtypes that often present clinically with nephritic features shown. FSGS, focal segmental glomeruloslcerosis; GS, glomerulosclerosis; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis

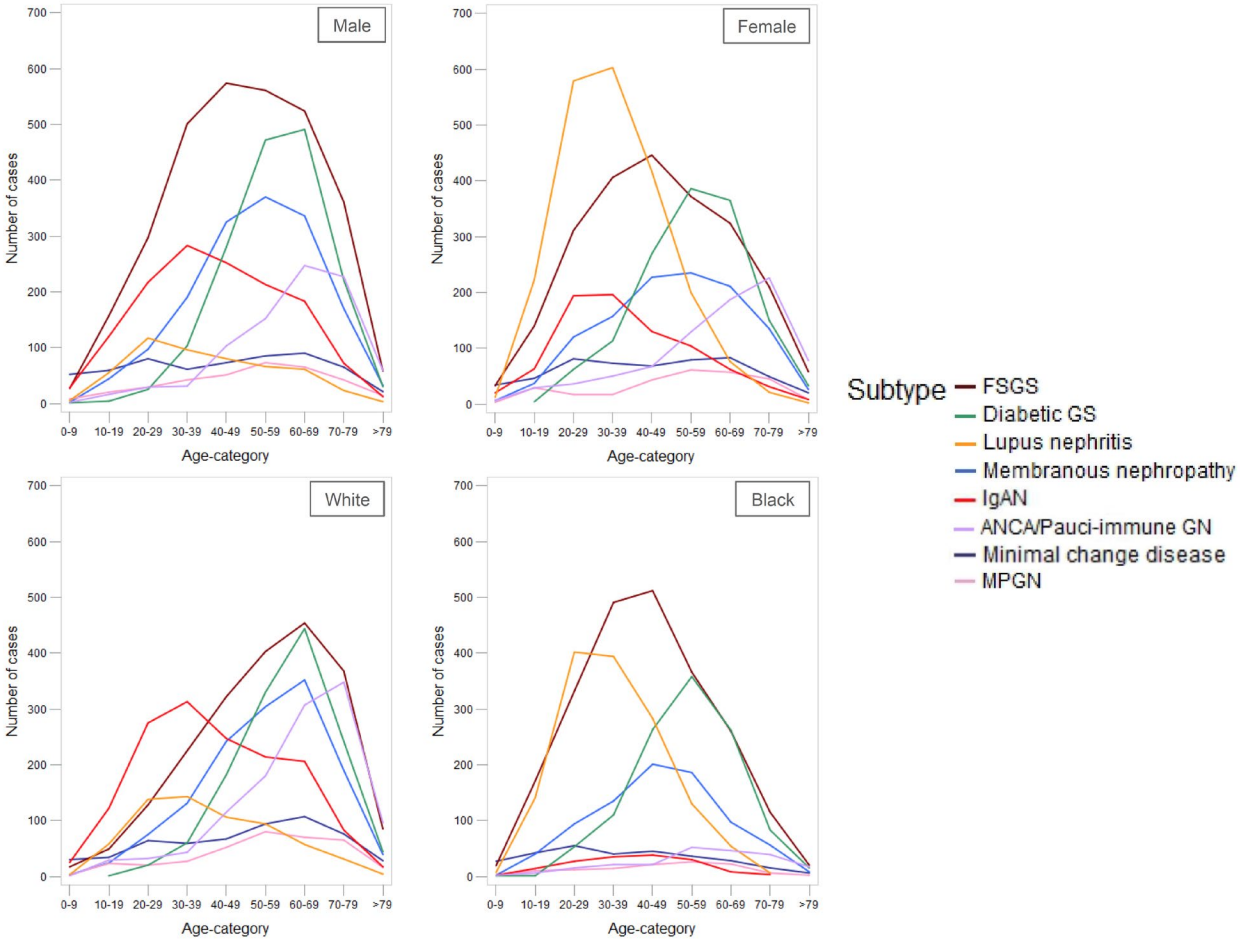

Figure 3: Absolute renal biopsy diagnosis frequencies of the most common glomerular disease subtypes according to patient age category, stratified by sex and race. FSGS, focal segmental glomeruloslcerosis; GS, glomerulosclerosis; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis

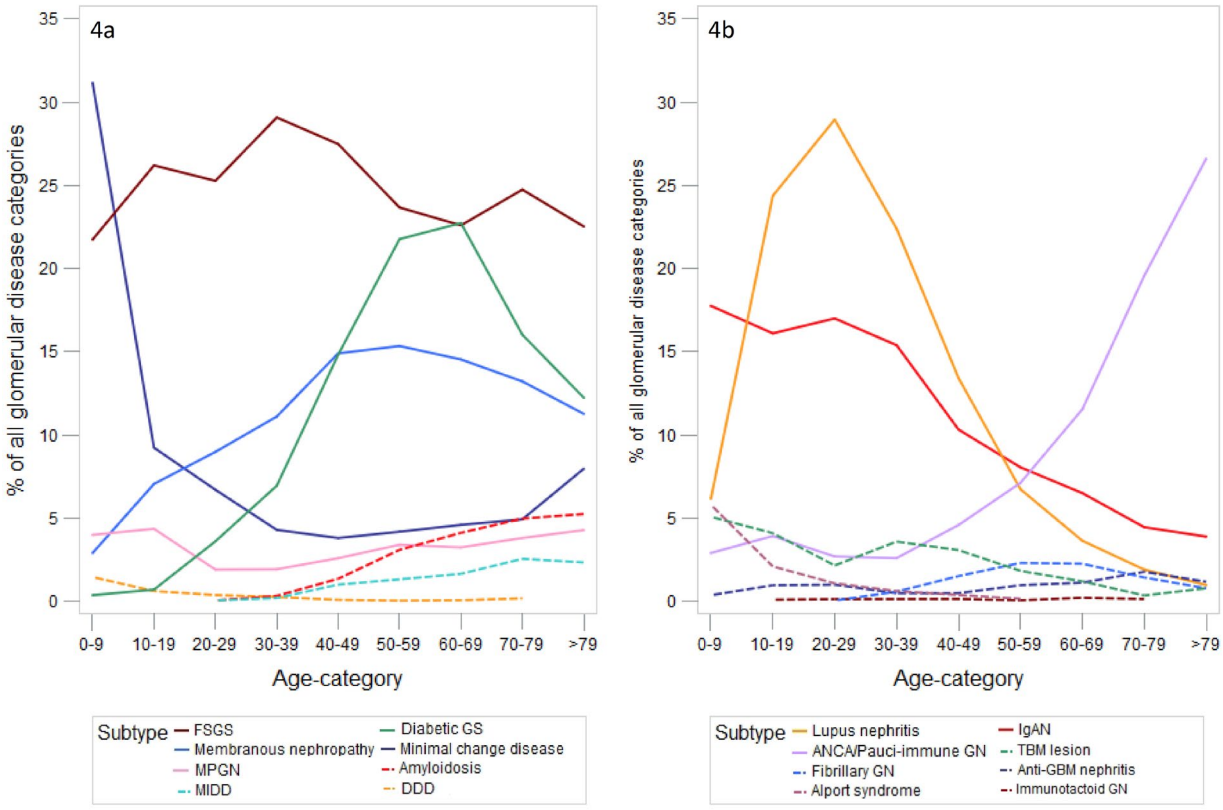

Figure 4: Proportion (%) of patients in each age group who have the specified glomerular disease subtypes that typically present clinically with the nephrotic syndrome (Figue 4a) or nephritic features (Figure 4b). FSGS, focal segmental glomeruloslcerosis; GS, glomerulosclerosis; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.

Chapter 5. Patient Characteristics and Outcomes by GN Subtype in ESRD

Authors:

Michelle M. O'Shaughnessy MB BCh[1], Maria E. Montez-Rath PhD[1], Richard A. Lafayette MD[1], Wolfgang C. Winkelmayer MD ScD[2]

Affiliations:

[1] Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA

[2] Section of Nephrology, Baylor College of Medicine, Houston, TX

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5.1. Abstract

Background and objectives: Outcomes-based research rarely focuses on patients with end-stage renal disease (ESRD) due to glomerulonephritis (GN). We hypothesized that GN subtype would clinically discriminate patient groups and independently associate with survival after ESRD therapy initiation.

Design, setting, participants, & measurements: Data were extracted from the US Renal Data System for adult patients with incident (1996-2011) ESRD attributed to six GN subtypes: focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membranoproliferative GN (MPGN), lupus nephritis (LN), and vasculitis. ESRD attributed to diabetes (DN) and autosomal dominant polycystic kidney disease (ADPKD) served as non-GN comparators. Unadjusted and adjusted mortality hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox regression (reference=IgAN). Models sequentially adjusted for socio-demographic (Model 2), comorbidity/laboratory (Model 3), and ESRD treatment modality (Model 4) variables.

Results: Among 84,301 patients with ESRD attributed to GN, median age ranged from 39 (LN) to 66 (vasculitis) years, male gender from 18% (LN) to 68% (IgAN), and African-American race from 7% (IgAN) to 49% (LN). Patients with IgAN had the fewest comorbidities and lowest use of haemodialysis (70.1%). After a median follow-up of 2.5 (IQR 1.0-4.9) years, crude mortality was lowest in IgAN (3.7 deaths/100 person-years). Compared to IgAN, adjusted mortality was significantly higher in LN (Model4 aHR=1.75, 95%CI 1.68-1.83)—quantitatively similar to in DN (aHR=1.73, 95%CI 1.67-1.79)—as well as in all other GN subtypes (MN: aHR=1.23, 95%CI 1.17-1.29; FSGS: aHR=1.37, 95%CI 1.32-1.42; MPGN: aHR=1.38, 95%CI 1.31-1.45; vasculitis: aHR=1.51, 95%CI 1.45-1.58) and in ADPKD (aHR=1.22, 95%CI 1.18-1.27).

Conclusions: This study exposes substantial heterogeneity across GN subtypes at ESRD therapy initiation and identifies independent associations between GN subtype and post-ESRD mortality. These survival discrepancies warrant further study and the utility of current research practice to group GN subtypes together when evaluating ESRD outcomes should be questioned.

5.2. Introduction

Glomerulonephritis (GN) is the third most common cause of end-stage renal disease (ESRD) in patients initiating dialysis or receiving a kidney transplant in the United States. In the most recent Annual Data Report of the United States Renal Data System (USRDS), GN accounted for 6.3% of patients initiating ESRD therapy in 2011, trailing only diabetes (43.9%) and hypertension (27.8%), and patients with GN comprised 14.3% of the prevalent treated ESRD population.[110] Treatment of patients with ESRD due to GN incurs an estimated annual cost to Medicare alone of almost three billion dollars.[110] Mortality in GN increases dramatically after the onset of ESRD,[111-114] yet the relative contributions from generic ESRD-related factors and from the underlying cause of GN to this finding have not formally been evaluated.

The USRDS adopts GN as one of four major cause-of-ESRD stratification variables in published reports, along with diabetes, hypertension and cystic kidney disease. However, when juxtaposing the characteristics and outcomes of patients with GN to those with other causes of ESRD, it is important to consider that GN is not a single disease entity but rather a broad disease category comprised of histologically and clinically distinct GN subtypes. Alongside differing renal manifestations, heterogeneity across GN subtypes with respect to systemic comorbidities and mortality has been identified in non-ESRD populations.[42,115] Whether these phenotypic and prognostic distinctions diverge or converge after ESRD development remains largely unknown.

We conducted this present study to examine differences among GN subtypes with respect to demographic and clinical attributes at presentation to ESRD and prognosis after initiation of ESRD therapy. We posit that exploring any such differences would serve to elucidate and quantify long-term disease-specific risks, explain post-ESRD survival discrepancies between GN and non-GN patient groups, and facilitate the development of a more individualized and equitable patient care approach.

5.3. Study population and methods

Study Population and Data Sources:

All adult patients aged ≥18 years who initiated ESRD therapy with haemodialysis, peritoneal dialysis, or kidney transplantation between 1/1/1996, and 12/31/2011, were retrospectively identified from the USRDS, a national registry of almost all patients with treated ESRD. Patients with ESRD attributed to one of six common GN subtypes—focal segmental glomerulonephritis (FSGS), IgA nephropathy (IgAN),

membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), lupus nephritis (LN), and vasculitis—were selected as the principal study cohort. These patients were identified using Cause of ESRD diagnostic codes (**supplemental appendix**) obtained from Medical Evidence Reports (form CMS-2728). These reports are submitted by attending nephrologists to the Centres for Medicare and Medicaid Services within 45 days of a patient commencing ESRD therapy. Patients with ESRD attributed to diabetes (DN) and autosomal dominant polycystic kidney disease (ADPKD) were selected as non-GN comparator groups. Missing or uncertain cause of ESRD, or a defined cause other than the eight of interest, were the sole study exclusion criteria.

Patient Characteristics:

Baseline socio-demographic and clinical data were extracted from USRDS *Patient* and *Medical Evidence* files. Age, sex, race (white, African-American, Asian, other), Hispanic ethnicity (yes/no), Medicaid insurance (yes/no), and geographic region (Northeast, Midwest, South, West) were selected as socio-demographic variables. Initial ESRD therapy modalities were defined as haemodialysis, peritoneal dialysis, or kidney transplantation, using USRDS-defined codes (**supplemental appendix**). Date of first kidney transplantation was also obtained for patients initiating ESRD therapy with dialysis. Baseline comorbidities (reported in Medical Evidence Reports to be present currently or within the past 10 years) included diabetes, heart failure, coronary heart disease, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, current smoking, cancer, peripheral vascular disease, and non-ambulant status (unable to ambulate or to transfer). Laboratory values (reported in Medical Evidence Reports as measured within 45 days prior to commencing ESRD therapy) included albumin, haemoglobin, and creatinine (used to calculate Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate, eGFR).

Outcomes:

Death was our primary study outcome. Cause of death (reported on CMS-2746 *Death Notification Forms*), using collapsed USRDS-defined categories (**supplemental appendix)**, was a secondary outcome. Date and cause of death were ascertained from USRDS *Patient* files. Patients were censored at end of study (1/1/2012)

Statistical Analyses:

Cross tabulation and distribution plots were used to examine unadjusted differences in baseline characteristics between groups. Categorical variables were summarized as frequencies and proportions and continuous variables as medians and interquartile ranges, or as means and standard deviations, as appropriate. Differences in mortality were examined using time-to-event analysis. Cumulative survival curves were derived by the Kaplan-Meier method and compared using the log-rank test. Mortality hazard ratios (HRs) with 95% confidence intervals (CI) were estimated using Cox proportional hazards regression, stratified by year of ESRD therapy initiation, with IgAN as the referent group. Model 1 = unadjusted; Model 2 = adjustment for socio-demographic characteristics (age, sex, race, ethnicity, Medicaid insurance); Model 3 = additional adjustment for baseline comorbidity and laboratory variables. To adjust for ESRD therapy modality at baseline and subsequent access to transplantation, we fitted a fourth model (Model 4) that added to model 3 baseline modality as a fixed covariate and post-ESRD transplantation as a time-dependent covariate. This allowed patients who initiated ESRD therapy with dialysis but later received a transplant to obtain a second ESRD treatment record starting on the transplant date. Squared terms were included for all continuous variables (age and laboratory values). Proportionality was examined using plotted log (-log) survival curves.

Approximately 32% of patients had at least one missing variable. To handle these missing data, we assumed them to be missing at random (MAR) and used standard multiple imputation (MI) techniques to impute up to 32 datasets.[116] In addition to including all Model 4 covariates, the imputation model included the event indicator and the Nelson-Aalen estimator of the cumulative marginal hazard *H(T)*, where T is the time to event or censoring.[117] Imputations were performed separately by year of ESRD therapy initiation and assumed a joint modelling approach.[118] Log HR from the models applied to each imputation dataset were then combined, as described by Little and Rubin.[119] As a sensitivity analysis, models were repeated using complete case analysis.

All data were analysed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). This study was approved by an Internal Review Board of Stanford University School of Medicine.

5.4. Results

The final study population comprised 84,301 patients with ESRD attributed to six major GN subtypes: 34,330 (40.7%) with FSGS; 13,012 (15.4%) with IgAN; 7,177 (8.5%) with MN; 5,193 (6.2%) with MPGN;

16,463 (19.5%) with LN; and 8,126 (9.6%) with vasculitis (**Figure 1**). In addition, 36,272 patients with ADPKD and 720,001 patients with (DN) were studied as external non-GN comparator groups.

Socio-demographic characteristics varied across GN subtypes (**Table 1**). Median age ranged from 39 (LN) to 66 years (vasculitis). There were approximately twice as many men as women within all primary GN subtypes, ranging from 60% male in MPGN to 68% male in IgAN. Sex was balanced in vasculitis (52% male) and women predominated in LN (18% were men). African-American race was over-represented in LN (48.6%) and FSGS (36.2%), Asian race was over-represented in IgAN (15.4%), and White race was over-represented in vasculitis (88.8%). Medicaid insurance was most common in LN (31.0%).

Baseline reported comorbidity and laboratory characteristics differed among GN subtypes. Congestive heart failure (8.3%), cerebrovascular disease (2.4%) and peripheral vascular disease (2.9%) were least common in IgAN, while diabetes (8.9%), atherosclerotic heart disease (6.3%), and cancer (1.6%) were least common in LN. Serum albumin was highest in IgAN (3.5 ±0.7 g/dL) and lowest in MN (2.9 ±0.9 g/dL). Haemoglobin was highest in IgAN (10.1 ±1.9 g/dL) and lowest in LN (9.4 ±1.8 g/dL).

Among non-GN comparator groups, patients with ADPKD had a relatively favourable comorbidity and laboratory profile, comparable to that in IgAN. Patients with DN had the highest comorbidity burden of all, although haemoglobin and albumin levels were higher than in some GN subtypes.

The proportion of patients receiving a pre-emptive kidney transplant was substantially higher in IgAN (11.9%) than in LN (3.1%) and vasculitis (1.5%). Use of peritoneal dialysis as an initial ESRD therapy was also higher in IgAN (16.8%) than in LN (10.8%) and vasculitis (6.5%).

On follow-up, 84,301 patients with ESRD attributed to GN contributed 431,657 person-years of observation, during which time 33,774 deaths were observed (crude mortality rate 7.8/100 person-years). Unadjusted five-year survival ranged from 45.5% (95% CI 44.2-46.7%) in vasculitis to 81.5% (95% CI 80.7-82.2%) in IgAN, as illustrated in Kaplan Meier survival plots **(Figure 2)**. These survival curves corresponded to mortality rates ranging from 3.69 (95% CI 3.56-3.83) per 100 person years in IgAN to 15.91 (95% CI 15.45-16.36) per 100 person years in vasculitis (**Table 2**). Survival discrepancies are further reflected in unadjusted hazard ratios for mortality (**Figure 3 and Supplemental Table S1**), which differed by more than 4-fold across GN subtypes (HR of 4.15, 95% CI 3.96-4.35 in vasculitis). Adjustment for socio-demographic characteristics attenuated hazard ratios in all subgroups except for LN, such that LN became the GN subtype associated with the highest socio-demographic-adjusted mortality (Model 2).

Additional adjustment for baseline comorbidity and laboratory characteristics (Model 3) and for ESRD therapy modality, including time-varying adjustment for kidney transplantation (Model 4), attenuated hazard ratios further within all GN subtypes, as compared to IgAN. Even after accounting for these differences in case mix, however, pronounced mortality differences across GN subtypes persisted. Compared to patients with ESRD due to IgAN, adjusted (Model 4) mortality hazards were 23% (95%CI 17%-29%), 37% (95%CI 32%-42%), 38% (95%CI 31%-45%), 51% (95%CI 45%-58%), and 75% (95%CI 68%-83%) higher in MN, FSGS, MPGN, vasculitis and LN, respectively. Adjusted mortality in IgAN was also lower than in ADPKD (aHR=1.22, 95%CI 1.18-1.27), a disease with a generally favourable prognosis in ESRD,[120,121] whereas mortality in LN (aHR=1.75, 95%CI 1.68-1.83) was similar to in DN (aHR=1.73, 95%CI 1.67-1.79), a disease with a particularly poor prognosis in ESRD.[122]

We observed some differences across GN subtypes with respect to primary cause of death (**Figure 4 and Supplemental Table S2**). Cardiovascular disease accounted for the highest proportion of deaths within all GN subtypes, ranging from 34.2% in vasculitis to 44.6% in FSGS. The highest proportion of infection-related deaths was observed in LN (14.0%), comparing to rates of 10.6% or less among primary GN subtypes. Malignancy-related deaths were comparatively rare, ranging from 2.3% in LN to 6.5% in MN.

Sensitivity analysis: imputed versus complete data analysis

Due to computational limitations we were unable to generate 32 imputed datasets to reflect our 32% missing data frequency, as previously suggested.[116] Instead, we generated results using 8 and 15 imputed datasets. As summarized in **Supplemental Table S1** and **Supplemental Figure S1**, complete case analyses tended to yield somewhat larger associations compared with multiply imputed analyses. Results did not materially change when increasing from 8 to 15 imputed datasets, suggesting that additional efficiency was unlikely to be gained by extending imputation beyond 15 datasets.

5.5. Discussion

In this large, national, study of patients with ESRD attributed to GN who initiated dialysis or received a pre-emptive kidney transplant between 1996 and 2011, we identified considerable socio-demographic and clinical differences across six important GN subtypes. We also observed marked survival discrepancies that persisted even after adjustment for socio-demographic and clinical factors. Some GN subtypes (e.g. IgAN) conferred a particularly favourable prognosis, superior to that in ADPKD, whereas others (e.g. LN) displayed shortened survival, similar to in patients with ESRD due to diabetes. The most

obvious conclusion to draw from these findings is that combining GN subtypes into a single disease category, as is current practice in research and public health reporting, is of questionable utility; this approach fails to recognize the heterogeneity and complexity pervading this patient group.

Our study is not the first to report differential survival outcomes across GN subtypes. A single-centre, retrospective study of 580 Taiwanese patients with biopsy-proven GN, not yet requiring dialysis (mean eGFR 70.4 ±33.8 ml/min/1.73m^2), reported a lower baseline comorbidity and cytotoxic treatment burden in patients with IgAN than with MN or FSGS.[42] Unadjusted mortality, after a median follow-up of 5.9 years, was significantly lower in IgAN (4.6%) as compared to MN (17.2%) and FSGS (14.4%); however, adjustment for between-group demographic and clinical differences was not performed and outcomes after ESRD development were not examined. A second study of 1,943 Korean patients with primary GN again demonstrated a survival advantage in IgAN as compared to MN, FSGS, and MPGN.[115] In the subset of patients who developed ESRD (n=257), 10-year survival risks of 85%, 80% (approximately), 61%, and 26%, respectively, were reported. Mortality comparisons accounting for case mix differences were, again, not performed. With the exception of this sub-group analysis, most other studies examining mortality outcomes after ERSD development in GN were restricted to single GN subtypes [65,66,112,123] or combined subtypes into a single GN category,[67,124] precluding direct comparisons across GN subtypes.

The present study translates these previous findings, derived from non-ESRD, non-U.S., patient populations, to a nationally representative cohort of U.S. patients with treated ESRD. It expands upon prior studies by comparing outcomes not only across primary GN subtypes but also across secondary GN subtypes and non-GN related causes of ESRD. Importantly, this study also addresses the question of whether GN subtype is independently associated with post-ESRD survival, or whether mortality differences are explained by differences in case mix alone. We confirm that post-ESRD survival in IgAN not only exceeds survival in other primary GN subtypes but also exceeds survival in secondary GN subtypes and in ADPKD. This latter finding conflicts with prior reports suggesting inferior survival in GN as compared to ADPKD. For example, a study of 44,240 Brazilian patients with treated ESRD reported a demographic-adjusted relative risk (RR) for mortality, with reference to hypertension-associated ESRD, of 0.93 (95% CI 0.89-0.98) in GN as compared to 0.69 (95% CI 0.61-0.78) in ADPKD.[67] Within the U.S., one-year mortality is reportedly two-fold higher in primary GN than in cystic renal disease (10% versus 5%, respectively).[110] Our data explain these findings by demonstrating a spectrum of risk within GN: patients with IgAN have a survival advantage over patients with ADPKD that is counter-balanced by a

survival disadvantage in other GN subtypes. This finding escapes detection when individual GN subtypes are combined together in ESRD outcomes research.

The substantially higher mortality observed in patients with LN in this study warrants further mention. High rates of infection,[125-127] cardiovascular disease,[128] and hospitalization[126,128] were previously described in patients with ESRD due to LN, although direct comparisons to other GN subtypes are largely lacking and studies investigating mortality report conflicting findings.[71,126,128-131] We determined that unadjusted crude mortality in LN exceeded mortality identified in many other GN subtypes, despite this being the youngest patient group with the highest proportion of African American and female patients, factors which should have portended a favourable prognosis.[132] Indeed, adjustment for socio-demographic factors uniquely increased the relative risk for mortality in LN with respect to IgAN, in contrast to the risk attenuation that was observed in all other GN subtypes (**Figure 3**). Further adjustment for differences in clinical characteristics, including access to kidney transplantation, reduced the hazard ratio for mortality in LN somewhat but it remained almost 2-fold higher than in the referent group, IgAN.

Our study has several limitations. First, we cannot confirm the validity of GN subtype designations obtained from the USRDS. A previous study measured agreement between biopsy-based diagnoses and USRDS-derived diagnoses among 227 patients with biopsy-proven GN.[21] Poor overall agreement was largely explained by "missing" (57%) and "GN not histologically examined" (9%) diagnoses submitted to the USRDS; positive predictive values exceeded 90% once a specific GN subtype was selected. Agreement also improved after 1995, following revisions to the Medical Evidence Report diagnostic coding system in that year. Nevertheless, we could not always distinguish primary from secondary forms of GN (e.g. primary from secondary MN), nor are our study findings necessarily applicable to non-biopsied or misclassified patients with GN (i.e. false negatives) who may differ fundamentally from correctly classified patients. Second, as a retrospective observational study, associations between GN subtype and mortality cannot be assumed to represent causation. We could not distinguish the influence of GN-related factors (e.g. nephrotic syndrome, systemic inflammation, or immunosuppressive therapy) from unmeasured or residual non-GN related factors. Some misclassification of comorbidities is likely (e.g. diabetes was reported in only 88% of patients with ESRD due to diabetes), and detailed socio-economic data were not available: however, we propose that misclassification of these confounding variables is likely to be non-differential, and to bias findings toward the null. At the same time, adjustment for laboratory variables and initial ESRD treatment modality may "over-adjust" for disease

mediators, particularly in those GN subtypes that typically display a more rapid and unpredictable course to ESRD (e.g. LN, vasculitis). We were interested to note that albumin was lowest in the GN subtypes most typically associated with nephrotic syndrome (MN, MPGN) and systemic inflammation (LN, vasculitis), while haemoglobin was lowest in those GN subtypes most likely to be treated with immunosuppressive therapy (LN, vasculitis), suggesting direct disease- and treatment-mediated effects. Finally, our findings apply to patients with progressive GN who survive to ESRD and should not be generalized to patients with mild, treated, or remitted GN without ESRD, or to patients who die before developing ESRD.

Despite these limitations, our study has a number of strengths. We report findings derived from population-based data that are broadly applicable to all patients with ESRD attributed to GN receiving dialysis or with a functioning kidney transplant in the US. Study investigators did not collect primary data or adjudicate outcomes, virtually eliminating investigator bias. We employed sophisticated statistical techniques to overcome shortfalls inherent to observational study design, including multiple imputation methods to handle missing data and use of sequentially adjusted models to minimize confounding.

In summary, we have identified in a large, nationally-representative, ESRD cohort that patients classified into individual histologic GN subtypes differ considerably from one another with respect to socio-demographic, clinical, laboratory, and ESRD therapy modality characteristics. We furthermore determined that GN subtype independently associates with survival after initiation of ESRD treatment, even after accounting for differences in case mix. We propose that GN subtype be addressed in all future studies of patients with ESRD due to GN, to elucidate explanations for observed survival differences and to identify modifiable factors amenable to targeting in interventional trials and public health strategies.

5.6. Tables and figures (subsequent pages)

Table 1: Baseline characteristics, according to glomerulonephritis (GN) subtype

Characteristic	Primary GN Subtypes				Secondary GN Subtypes		Non-GN Comparator Groups	
	FSGS	IgAN	MN	MPGN	LN	Vasculitis	DN	ADPKD
N (% among GN types)	34,330 (40.7)	13,012 (15.4)	7,177 (8.5)	5,193 (6.2)	16,463 (19.5)	8,126 (9.6)	720,001 (n/a)	36,272 (n/a)
Age, median (IQR), years	51 (38-65)	44 (33-57)	59 (47-71)	53 (41-65)	39 (29-50)	66 (54-75)	63 (54-72)	54 (47-64)
Sex (male), %	61.6	67.6	66.0	60.4	18.2	52.4	52.2	54.0
Race, %								
White	59.0	75.1	69.5	74.5	43.4	88.8	64.9	82.0
Black	36.2	6.6	26.0	18.1	48.6	7.5	27.8	13.1
Asian	3.5	15.4	3.0	4.9	5.8	1.9	4.4	3.8
Other	1.4	2.9	1.5	2.4	2.1	1.8	2.8	1.0
Hispanic ethnicity, %	8.6	12.4	10.0	10.6	16.2	8.9	17.1	8.6
Medicaid insured, %	18.4	13.4	16.5	20.2	31.0	11.9	28.3	12.5
ESRD therapy, %								
Hemodialysis	78.4	70.1	82.0	80.9	85.5	91.6	91.4	70.5
Peritoneal dialysis	14.5	16.8	12.8	11.6	10.8	6.5	7.1	15.6
Transplant	6.1	11.9	4.2	6.3	3.1	1.5	0.9	12.7
Missing	1.0	1.3	1.0	1.2	0.7	0.4	0.6	1.2
Geographic region, %								
North-East	20.0	19.6	20.4	20.9	16.1	19.3	16.8	19.7
Mid-West	23.3	23.0	23.6	24.7	18.4	27.2	20.5	22.9
South	39.6	30.3	37.9	32.9	44.1	33.2	39.8	36.1
West	16.6	26.6	17.0	20.5	20.3	20.0	20.9	20.2
Missing	0.6	0.5	1.2	1.0	1.1	0.3	2.0	1.1
Comorbidities, %								
Diabetes	13.3	9.3	15.0	14.9	8.9	15.9	88.0	7.5
Heart failure	14.6	8.3	18.8	17.9	15.0	18.2	38.5	8.4
Coronary heart disease	12.2	6.5	15.2	10.6	6.3	14.5	28.1	9.6

Cerebrovascular event	4.1	2.4	5.7	4.2	5.2	5.3	10.5	4.3
Hypertension	78.5	79.1	78.3	77.7	75.1	67.3	81.1	79.8
COPD	5.7	2.7	7.2	6.8	2.4	10.2	7.6	3.5
Current smoker	7.4	4.8	7.2	8.5	4.2	4.4	4.7	5.8
Cancer	4.8	2.8	6.2	5.7	1.6	6.0	3.9	3.6
PVD	5.1	2.9	6.2	5.0	3.5	7.6	19.8	3.4
Non-ambulant	1.6	0.9	2.6	2.2	2.4	3.5	6.6	1.0
Laboratory measurements, mean (SD)								
Albumin, g/dL	3.3 (0.8)	3.5 (0.7)	2.9 (0.9)	3.0 (0.8)	2.9 (0.8)	3.0 (0.7)	3.1 (0.7)	3.8 (0.6)
Albumin missing, %	23.1	22.5	22.3	22.3	23.6	23.2	25.5	23.4
Haemoglobin, g/dL	10.1 (1.8)	10.1 (1.9)	10.0 (1.8)	9.9 (1.8)	9.4 (1.8)	9.6 (1.7)	9.9 (1.6)	10.5 (1.8)
Hemoglobin missing, %	11.4	11.5	11.4	11.7	9.9	10.6	10.5	11.7
Creatinine, mg/dL	8.4 (4.2)	8.4 (4.0)	7.7 (3.8)	7.4 (3.7)	7.4 (3.5)	7.5 (3.6)	6.3 (2.8)	7.6 (3.3)
Creatinine missing, %	2.0	1.5	1.6	1.8	1.4	1.1	1.2	1.4
eGFR, ml/min/1.73m2	8.7 (4.1)	8.4 (4.0)	9.2 (4.5)	9.5 (4.6)	9.4 (4.6)	8.7 (4.3)	10.6 (4.7)	8.5 (3.8)
eGFR missing, %	2.6	2.1	2.6	2.9	2.5	1.7	2.2	2.0

FSGS, focal segmental glomerulosclerosis; LN, lupus nephritis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN, DN, diabetes related ESRD; ADPKD, autosomal dominant polycystic kidney disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; eGFR, glomerular filtration rate, using the 4-variable Modification of Diet in Renal Disease (MDRD) formula.

Table 2: Follow-up details of study population, including unadjusted mortality rates, by GN subtype

GN subtype	Number of patients (%)	Person time at risk, years	Number of deaths (%)	Mortality rate per 100 person-years (95% confidence interval)
IgAN	13,012 (15.4)	76,901	2,839 (21.8)	3.69 (3.56-3.83)
FSGS	34,330 (40.7)	179,364	13,721 (40.0)	7.65 (7.52-7.78)
LN	16,463 (19.5)	84,585	6,741 (41.0)	7.97 (7.78- 8.16)
MPGN	5,193 (6.2)	26,869	2,405 (46.3)	8.95 (8.59-9.31)
MN	7,177 (8.5)	34,482	3,382 (47.1)	9.81 (9.48-10.14)
Vasculitis	8,126 (9.6)	29,456	4,686 (57.7)	15.91 (15.45-16.36)

IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; LN, lupus nephritis; MPGN, membranoproliferative GN; MN, membranous nephropathy.

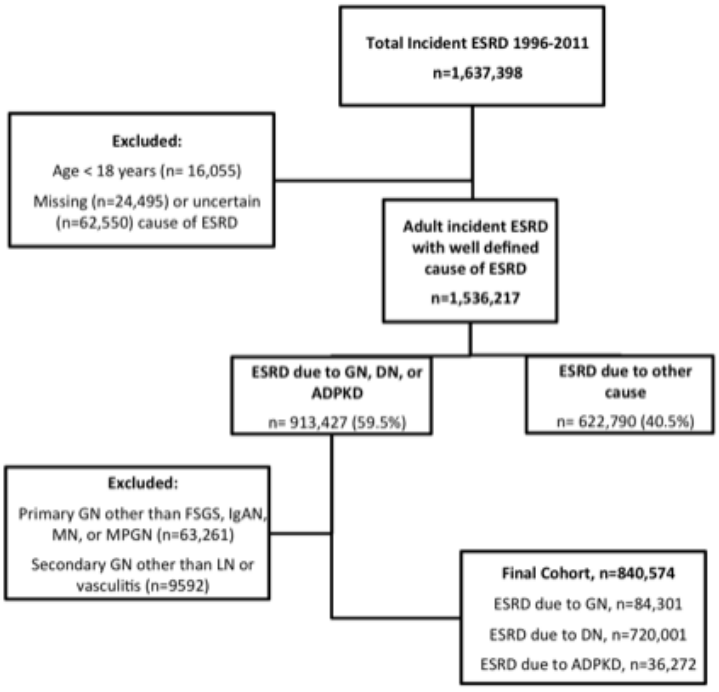

Figure 1: Flow diagram of cohort assembly. ESRD, End stage renal disease; GN, glomerulonephritis; DN, diabetes related ESRD; ADPKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; LN, lupus nephritis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN.

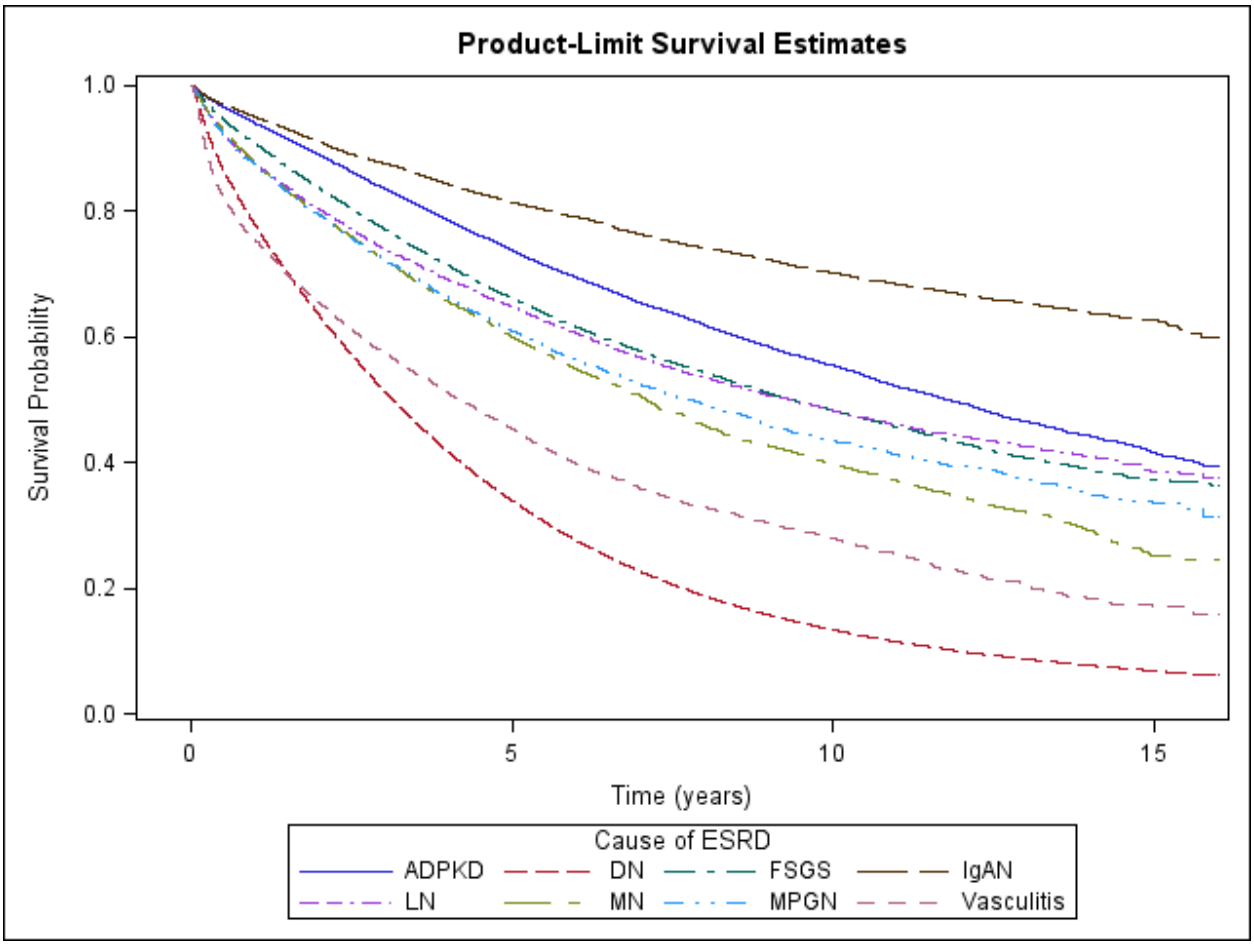

Figure 2: Kaplan Meier survival curves comparing patient survival by cause of ESRD. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetes related ESRD; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MN, membranous nephropathy; MPGN, membranoproliferative GN.

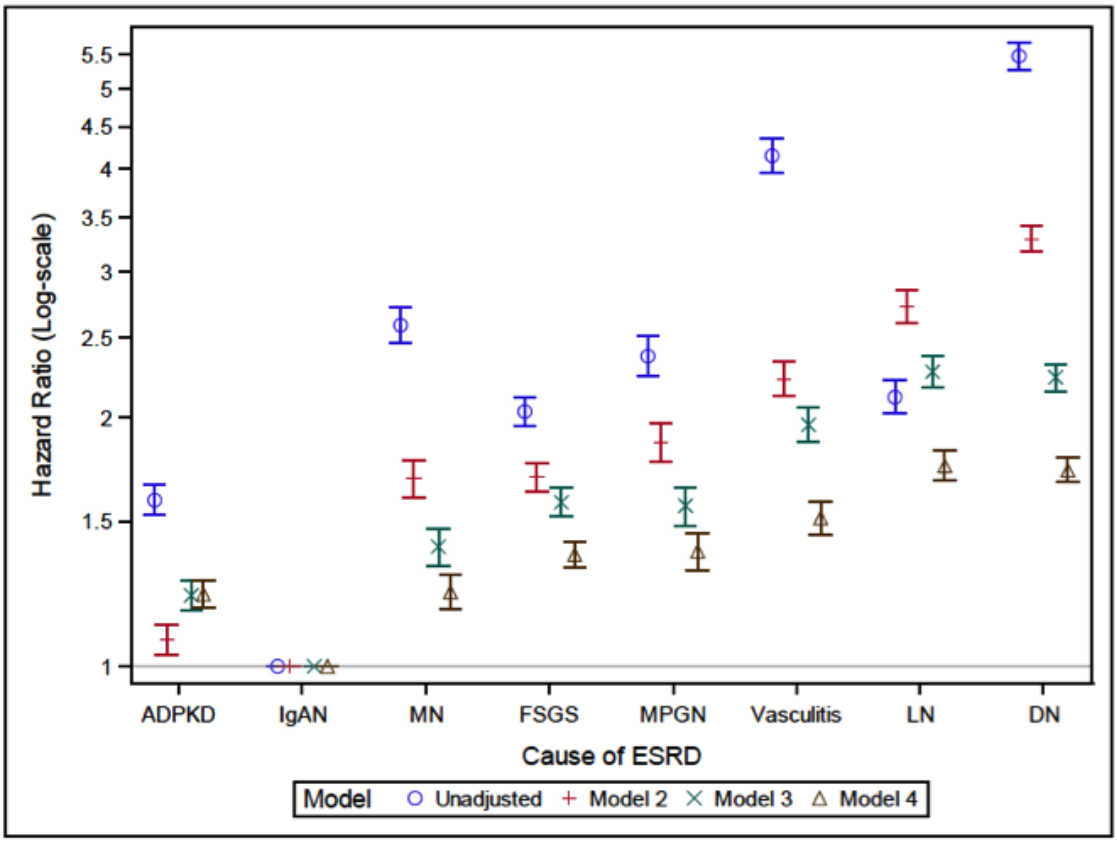

Figure 3: Unadjusted and adjusted mortality hazard ratios. Model 1: unadjusted; model 2: demographic adjusted; model 3: demographic and comorbidity adjusted; model 4: demographic, comorbidity and ESRD therapy modality adjusted. ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; LN, lupus nephritis, DN, diabetes related ESRD.

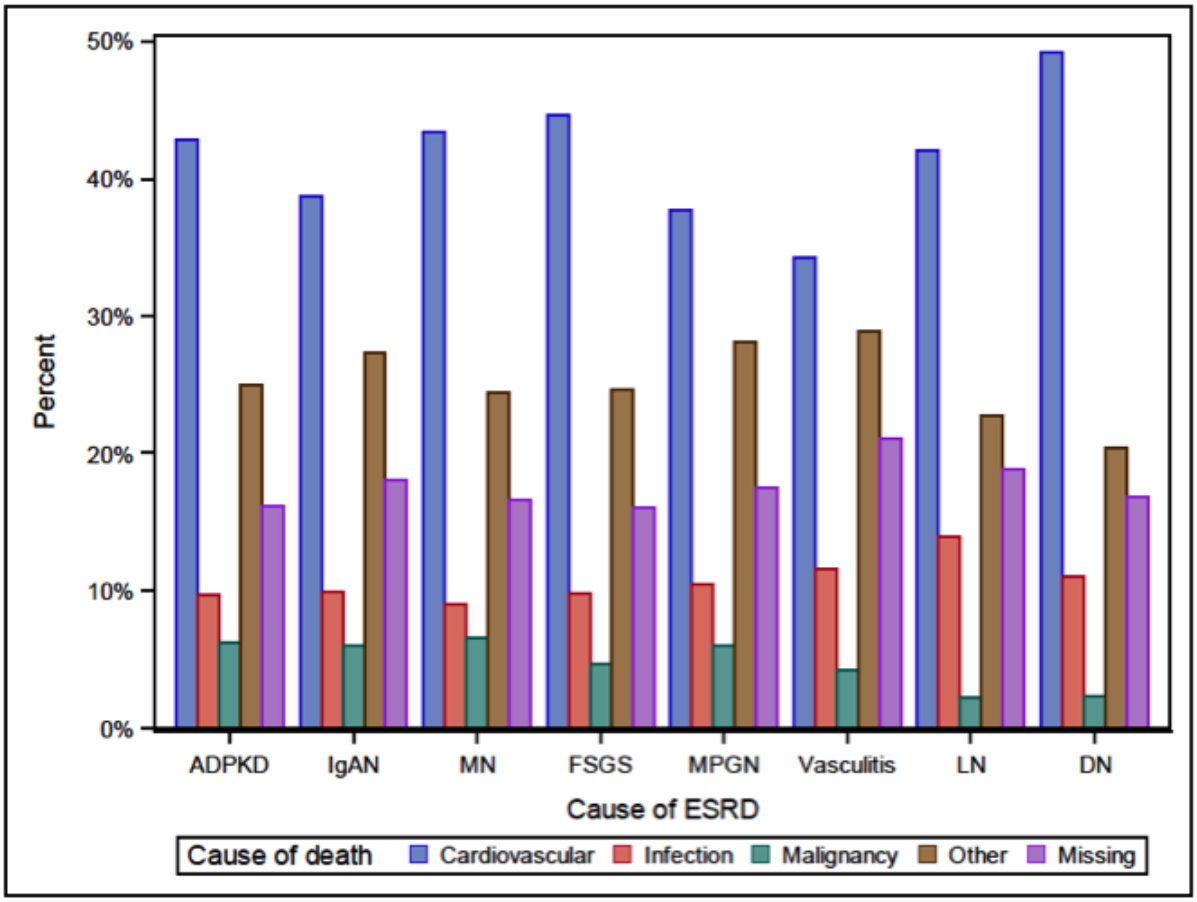

Figure 4: Cause of death categories, by GN subtype. ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; LN, lupus nephritis, DN, diabetes related ESRD.

Chapter 6. Cause of kidney disease and cardiovascular events in a national cohort of US patients with end-stage renal disease on dialysis: a retrospective analysis.

Authors:

Michelle M. O'Shaughnessy MB BCh MS[1], Sai Liu MPH[1], Maria E. Montez-Rath PhD[1], Richard A. Lafayette MD[1], Wolfgang C. Winkelmayer MD ScD[2]

Affiliations:

[1]Division of Nephrology, Stanford University School of Medicine, Palo Alto

[2]Selzman Institute for Kidney Health, Section of Nephrology, Baylor College of Medicine, Houston

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6.1. Abstract

Aims: End-stage renal disease (ESRD) is a strong cardiovascular risk factor. We aimed to determine the extent to which cause of kidney disease independently contributes to this risk.

Methods: Using a national U.S. ESRD registry, we selected patients with 8 different causes of ESRD who initiated dialysis 1997-2014. We used proportional sub-distribution hazard models, with non-cardiovascular death or kidney transplantation as competing risks, to estimate hazard ratios (HRs) for a first composite cardiovascular event (myocardial infarction, ischemic stroke, or cardiovascular or cerebrovascular death), by cause of ESRD. The population was restricted to those using Medicare insurance at day 91 after dialysis initiation (when most patients become Medicare eligible). Outcomes were ascertained from Medicare claims or Death Notifications.

Results: Among the 658,168 patients identified, composite event rates ranged from 3.5/100 person-years in IgA nephropathy to 14.6/100 person-years in diabetic nephropathy. After adjusting for demographics, socioeconomic factors, comorbidities, dialysis modality, and laboratory values, cardiovascular event HRs differed significantly by cause of ESRD. Comparing to IgA nephropathy, the adjusted HR was highest for diabetic nephropathy (aHR=2.97, 95% CI 2.77-3.20), next highest for lupus nephritis (aHR=1.86, 95% CI 1.71-2.03), and thereafter ranged from 1.29 (95% CI 1.19-1.39) in autosomal dominant polycystic kidney disease to 1.67 (95% CI 1.52-1.83) in membranous nephropathy.

Conclusion: High cardiovascular event rates in dialysis patients vary considerably by cause of ESRD. Determining underlying reasons for these differences might provide new insights in to cardiovascular disease mechanisms as well as inform future drug development and clinical trial design.

6.2. Introduction

Patients with chronic kidney disease (CKD), and in particular end-stage renal disease (ESRD), have a dramatically increased risk for cardiovascular events.[133,134] However, whether cardiovascular event rates differ according to the underlying cause of kidney failure has not adequately been explored. Patients with glomerular diseases in particular might have unique risk factors for cardiovascular disease development, including systemic inflammation (e.g. in vasculitis or lupus nephritis), medication-related toxicity (e.g. corticosteroid-induced metabolic syndrome), or complications of the nephrotic syndrome (e.g. hyperlipidaemia or thrombophilia). Previously, cardiovascular event rates in patients with specific subtypes of glomerular disease were reported to be higher than in the general population.[17,68-70] However, whether this represents a glomerular disease-specific effect or is instead attributable to more general features common to all causes of kidney disease (e.g., impaired kidney function, proteinuria, metabolic derangements) has not been examined.

The United States Renal Data System (USRDS) – a national registry of virtually all patients who commence dialysis or receive a kidney transplant in the U.S. – offers an opportunity to study this important question. By "levelling the playing field" with respect to severity of kidney dysfunction, examining cardiovascular outcomes in a population of patients who uniformly have advanced ESRD might help to disentangle the influence of cause of kidney disease from that of more general kidney dysfunction. Identifying differences in cardiovascular event rates across patients with different underlying causes of ESRD might inform understanding of disease mechanisms as well as identify high risk patient groups to be targeted for cardiovascular care and for enrolment in future clinical trials.

We thus examined cardiovascular and cerebrovascular event rates after dialysis initiation among patients with ESRD attributed to any of 8 causes of ESRD [6 subtypes of glomerular disease, diabetic nephropathy (DN), or autosomal dominant polycystic kidney disease (ADPKD)] who initiated haemodialysis or peritoneal dialysis in the U.S. between 1997 and 2014. We aimed to identify independent associations between cause of ESRD and cardiovascular event frequencies after dialysis initiation, using national ESRD registry data.

6.3. Methods

Data sources:

The USRDS, incorporating Medicare Institutional (Part A) and Physician/Supplier (Part B) insurance claims data, was our primary data source. The USRDS contains records for virtually all patients who receive a kidney transplant or who are maintained on dialysis in the U.S. We obtained cause of ESRD, demographic characteristics, comorbidities, laboratory values, and body mass index (BMI) from *patient* and *medevid* files: these data are derived from Centres for Medicare & Medicaid Services (CMS) Medical Evidence Reports (Form CMS-2728) submitted by nephrologists within 45 days of a patient commencing a new ESRD treatment. We obtained initial ESRD treatment modality from the *rxhist60* file. We used US Census Bureau data to obtain socioeconomic factors at the residential ZIP code level, as a proxy for patient-level socioeconomic status. We used year 2000 Decennial Census data, or American Community Survey (ACS) 5-year data (2007-2011), respectively, for patients starting dialysis prior to or after 2006.[72,73] We obtained outcome data for non-fatal cardiovascular events from Medicare Institutional (Part A) and Physician/Supplier (Part B) files. We obtained outcomes data for cardiovascular and non-cardiovascular deaths from the *patient* file: these data are derived from the Death Notification (form CMS-2746) submitted by nephrologists when a patient receiving ESRD treatment dies.

MOS, SL, and MMR had full access to all the data in the study and each take responsibility for its integrity and the data analysis.

Patient population:

We identified all adult patients (≥18 years) who commenced haemodialysis or peritoneal dialysis in the U.S. between Jan 1^{st,} 1997 and Oct 1^{st,} 2014 and whose ESRD was reported to be due to any of 8 more common and distinct causes of kidney disease i.e. one of 6 glomerular disease subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), lupus nephritis (LN), or vasculitis], DN, or ADPKD. We excluded patients who were missing information on sex or on first ESRD treatment modality (i.e. not known to have started haemodialysis or peritoneal dialysis as a first ESRD treatment modality), who were aged >100 years, who resided outside of the continental U.S. (i.e. Alaska, Hawaii, or the American Territories) or who had a pre-emptive kidney transplant prior to receiving any maintenance dialysis. We also excluded patients who died, discontinued dialysis, received a kidney transplant, or did not yet have Medicare Parts A&B as their primary insurance within the first 90 days after dialysis initiation.

Exposure:

Cause of kidney disease was the primary exposure. We chose IgAN as our reference group, based on our prior report that mortality after dialysis initiation is lowest in this patient group.[135] Cause of ESRD was defined as that reported by treating nephrologists in patients' initial Medical Evidence Report. The cause does not need to be confirmed by kidney biopsy and only one "primary" cause of kidney disease, as determined by the treating nephrologist, is collected per patient (per instructions: "if there are several probable causes, please choose one as primary"). A prior validation study determined that selection of a glomerular disease subtype on the Medical Evidence Report had a high positive predictive value (>90%), but low sensitivity (≤30%), for detecting true biopsy-confirmed glomerular disease diagnoses.[21]

Outcomes:

Our main cardiovascular outcome was a composite of first myocardial infarction (MI), first ischemic stroke, or cardiovascular death, with follow-up time starting on day 91 after dialysis initiation. We defined MI as an ICD-9 code of 410.xx as a primary, or 410.x1 as a non-primary, hospitalization diagnosis code, or acute MI as a designated cause of death on a Death Notification (cause of death codes 02 or 23). We defined stroke as an ICD-9 code for ischemic stroke (433.x1, 434.x1) as a primary hospitalization diagnosis code, or stroke as a designated cause of death on a Death Notification (cause of death code 36). We defined cardiovascular death as any cardiovascular or cerebrovascular cause of death on a Death Notification, including cause of death codes 02 (myocardial infarction, acute), 23 (myocardial infarction, acute), 25 (pericarditis, incl. cardiac tamponade), 26 (atherosclerotic heart disease), 27 (cardiomyopathy), 28 (cardiac arrhythmia), 29 (cardiac arrest, cause unknown), 30 (valvular heart disease), 31 (pulmonary oedema due to exogenous fluid), 32 (congestive heart failure), or 36 (cerebro-vascular accident including intracranial haemorrhage). We also examined individual components of the composite outcome. Kidney transplantation and non-cardiovascular deaths were treated as competing events in our primary analyses, and as censoring events in a sensitivity analysis. We chose to model death and transplantation as competing rather than censoring events since death precludes the observation of a cardiovascular event and transplantation might alter its probability of occurrence.[136] Moreover, we have shown that death[135] and kidney transplantation[137] rates differ by cause of ESRD and thus the extent of informative censoring would differ by cause of ESRD, introducing further bias. Administrative censoring for patients who had not yet experienced a cardiovascular or competing event occurred at the first of: loss of Medicare A&B as primary insurance; survival without an event of interest to 5 years and 90 days after dialysis initiation; or end-of study (Dec 31st, 2014).

Covariates:

We considered temporal (year of dialysis initiation), demographic, socioeconomic, and clinical factors, measured at baseline (day of dialysis initiation), that could impact cardiovascular event rates as potential confounders. Demographic factors included age, sex, race (black, white, Asian, other), Hispanic ethnicity (yes/no), geographic region (Northeast, Midwest, South, West), and the following neighbourhood-level socioeconomic factors: percentage unemployed among those 16 years or older; percentage with less than a high-school education among those aged 25 years or older; percentage living below the federal poverty line; median household income; and median rent. Clinical factors at dialysis initiation included: comorbidities [diabetes, heart failure, coronary heart disease, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, current or recent smoking, cancer, peripheral vascular disease, and inability to ambulate], laboratory values [serum albumin, estimated glomerular filtration rate (eGFR), and haemoglobin], dialysis modality [haemodialysis or peritoneal dialysis] and body mass index. We calculated eGFR from reported serum creatinine and demographics at dialysis initiation, using the CKD-EPI equation.[138]

Statistical Analyses:

We examined unadjusted differences in baseline characteristics across cause of ESRD groups using cross tabulation and distribution plots. We summarized categorical variables as frequencies and percentages and continuous variables as means and standard deviations, or as medians and interquartile ranges, as appropriate.

We computed unadjusted rates of the composite and individual cardiovascular outcomes for each cause of ESRD, based on the number of events observed per person-year starting at day 91 after dialysis initiation. We used stacked cumulative incidence plots to illustrate the cumulative incidences of individual components of the composite outcome along with the competing events of kidney transplantation and death, using the cumulative incidence function modelled by flexible parametric models.[139,140] By this method, first occurring events are plotted, including: transplantation, non-CV death, CV death, non-fatal MI, and non-fatal stroke. For events occurring on the same day ("ties") we used the following prioritization algorithm: kidney transplantation, non-CV death, CV death, non-fatal MI, non-fatal stroke.

In order to account for the competing risks of kidney transplantation and death due to non-cardiovascular causes, we used the proportional sub-distribution hazard model (Fine and Gray) to

compute sub-distribution hazard ratios (HRs) and 95% confidence intervals (CIs) comparing causes of ESRD for each outcome separately, with IgAN as the reference group.[141] Models were stratified by year of dialysis initiation. The sub-distribution hazard is defined as the probability of the outcome event occurring at time t, given that the patient has not yet experienced an outcome event, but may have experienced a competing event (transplantation or death). Thus, the sub-distribution HR can be used to directly answer the question of whether patients with comparator causes of ESRD are more likely to experience a cardiovascular event when compared to those with IgAN, in patients who are either event-free or who have experienced the competing event (death or transplantation).[142] As a sensitivity analysis, we censored patients at death or kidney transplantation and used Cox proportional hazards regression to obtain cause-specific Hrs. Here, individuals with competing events are removed from the risk set at the time of the competing event and the hazard rate is being evaluated in subjects who are still alive and have not undergone transplantation.

For all analyses, we added covariates to regression models sequentially to account for confounding. Model 1 included cause of ESRD. Model 2 added demographics. Model 3 added socioeconomic characteristics. Model 4 added clinical characteristics i.e., comorbidities (including a prior history of coronary heart disease or cerebrovascular disease), dialysis modality, and BMI. Finally, model 5 added baseline laboratory values.

We used log(-log) plots of 1- cumulative incidence function and plots of Loess smoothed scaled Schoenfeld residuals to examine the proportional hazards assumption.[142,143] Besides visual interpretation of these plots, we also performed a global test combining zero-slope tests on the scaled Schoenfeld residuals plotted against time for each covariate in the model.[144]

Missing Data:

The frequency of missing covariate data ranged from <1% (e.g. Hispanic ethnicity) to 25% (serum albumin) and 32% of patients had at least one missing variable. Missing data were similarly distributed across all categories of the exposure variable. We assumed these data to be missing at random and used multiple imputation (MI) (using SAS proc mi) through the joint modelling approach to generate 30 imputed data sets.[116] Besides the event indicator and the Nelson-Aalen estimate of the cumulative hazard, the imputation model also included all variables in the fully adjusted model. As a sensitivity analysis, we also conducted a complete-case analysis, where subjects with any missing data were excluded.

Statistical analyses were performed using a combination of SAS version 9.4 (SAS Institute, Inc., Cary, NC) and Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX).

A Stanford University School of Medicine Institutional Review Board approved the study (IRB protocol number 17904). De-identified data were used throughout and patient consent was not required.

6.4. Results

Patient characteristics

We identified 658,168 adult patients with ESRD attributed to one of 6 glomerular disease subtypes (IgAN n=9828, FSGS n=27,029, MN n=5660, MPGN n=3718, LN n=12,398, vasculitis n=5023), DN (n=567,778) or ADPKD (n=26,734), who initiated haemodialysis or peritoneal dialysis in the continental US between Jan 1st, 1997 and Oct 1st, 2014, **Figure 1**. Baseline characteristics of the study cohort are summarized in **Table 1 (online only)**. Demographic characteristics differed considerably by cause of ESRD: average age ranged from 40.8 (SD 15.0) years in LN to 62.7 (SD 15.8) years in vasculitis; male sex ranged from 18.4% in LN to 66.7% in IgAN; black race ranged from 7.9% in IgAN to 52.3% in LN; and Hispanic ethnicity ranged from 7.8% in FSGS to 15.9% in DN. Use of peritoneal dialysis as a first ESRD treatment modality was highest in IgAN (24.4%) and lowest in DN (8.5%). Patients with IgAN, LN, and ADPKD had comparatively low comorbidity frequencies, whereas patients with DN had the highest comorbidity burden. Pre-existing atherosclerotic heart disease was reported in 6.0% of patients with LN, 7.4% of those with IgAN, 10.1-15.0% of those with ADPKD or any of the remaining glomerular disease subtypes, and 26.0% of those with DN. Pre-existing cerebrovascular disease was reported in 2.9% of patients with IgAN, 4.4-5.9% of those with ADPKD or remaining glomerular disease subtypes, and 10.5% of those with DN. Body mass index was highest, and obesity most frequent, in those with DN or FSGS. Patients with LN or DN resided in the socioeconomically poorest neighbourhoods.

Cardiovascular Outcomes: Unadjusted

Overall, 200,889 patients (31%) experienced the composite cardiovascular outcome (an MI, stroke, or cardiovascular death) during the first five years of follow-up. Unadjusted rates for the composite outcome ranged from 3.4 per 100 person years in IgAN to 14.4 per 100 person years in DN, **Table 2**. Among individual outcomes, 91,695 patients (14%) experienced a fatal or non-fatal MI, 36,125 (5%) experienced a fatal or non-fatal stroke, and 139,465 (21%) died from a presumed cardiovascular cause

during the first 5 years of follow-up. As observed for the composite outcome, event rates for all individual outcomes were lowest for patients with IgAN and highest for patients with DN, **Table 2.**

We next considered unadjusted event rates in a model that accounted only for first events, thus projecting a patient's expected clinical course following dialysis initiation according to their cause of ESRD. **Figure 2** and **Supplemental Table 1** show the cumulative incidences of cardiovascular outcomes and competing events (non-cardiovascular deaths or kidney transplantation) in the five years following dialysis initiation (starting at day 91). By 5 years and 90 days after dialysis initiation, 49.3% of patients with IgAN had received a kidney transplant, and of the remaining patients 10.3% had experienced a fatal or non-fatal cardiovascular event, and 10.0% had died from a non-cardiovascular cause. In contrast, only 8.1% of patients with DN had received a kidney transplant, and of the remaining patients 40.1% had experienced a fatal or non-fatal cardiovascular event and 25.2% a non-cardiovascular death. The 5-year cumulative incidences of any cardiovascular event (prior to kidney transplantation) were 16.3% in ADPKD and ranged from between 16.6% in LN and 23% in MN among the comparator glomerular disease subtypes i.e., higher than in IgAN (10.3%) and lower than in DN (40.1%) in all cases.

Cardiovascular Outcomes: Adjusted

Unadjusted and adjusted HRs for the composite event and each of the individual cardiovascular outcomes are shown in **Table 3**. Sequential adjustment for factors that might confound or explain associations between cause of ESRD and cardiovascular event rates generally attenuated the HR relative to IgAN (with the singular exception of LN, for which HRs increased after demographic adjustment but then decreased after further adjustment). Even in fully adjusted models, however, significant heterogeneity in HRs for cardiovascular outcomes according to cause of ESRD were observed, **Table 3 and Figure 3**. When compared to IgAN, patients with any other cause of ESRD were significantly more likely to experience the composite and each of the individual cardiovascular outcomes. For the composite outcome, the fully adjusted HR was highest for DN (aHR=2.97, 95% CI 2.77-3.20), next highest for LN (aHR=1.86, 95% CI 1.71-2.03), intermediary between 1.55 and 1.67 in the other 4 comparator glomerular diseases (FSGS, MN, MPGN, and vasculitis), and lowest in ADPKD at 1.29 (95% CI 1.19-1.39). Considering individual components of the composite, the relative hazards for MI, stroke, or cardiovascular mortality were also highest in DN (aHRs of 3.01, 3.47, and 2.44, respectively], but also significantly higher for all other subtypes of glomerular disease or for ADPKD when compared to IgAN, **Table 3 and Figure 3**.

Sensitivity analyses computing cause-specific HRs (whereby transplantation and non-cardiovascular deaths were handled as censoring rather than competing events) or including only patients without missing data (i.e. complete case analysis) did not materially alter findings**, Supplemental tables 2 and 3.**

6.5. Discussion

In this population-based study of 658,168 adult patients who initiated dialysis in the U.S. over the last 20 years, we identified significant associations between underlying cause of ESRD and cardiovascular and cerebrovascular event rates after dialysis initiation. The associations persisted even after careful adjustment for between-group differences in demographic, socioeconomic, and comorbidity characteristics (for example, younger age, female sex, and black race were considerably more frequent in patients with LN). Of particular interest, we determined significant heterogeneity across six individual glomerular disease subtypes, challenging the prevailing research paradigm to group these disease subtypes together when examining ESRD outcomes. We previously demonstrated that the adjusted hazard for all-cause mortality following dialysis initiation or kidney transplantation was lower in IgAN than in other glomerular disease subtypes, with the hazard being highest in patients with LN [135,137] . In this study, we begin to close the knowledge gaps created by our prior findings, by determining that differences in all-cause mortality might largely be explained by differences in cardiovascular morbidity and mortality across causes of ESRD. In doing so, we create new opportunities for scientific exploration, drug discovery, clinical trial design, and patient management approaches.

Prior studies examining cardiovascular outcomes in patients with glomerular disease with or without ESRD primarily focused on a single glomerular disease subtype rather than comparing across subtypes. In a population-level Danish study that compared cardiovascular outcomes in patients with LN to those in the general population, an almost 7-fold higher risk for ischemic heart disease overall, with a 19-fold higher risk among those undergoing renal replacement therapy, was observed.[69] However, comparisons to patients with other causes of kidney disease were not performed. Another study compared cardiovascular outcomes in US patients with ESRD due to LN to those in patients with any other cause of ESRD and failed to identify an increased risk in those with LN.[71] However, heterogeneity within the comparator group (e.g. distinguishing outcomes in those with ESRD due to IgAN from those with ESRD due to DN) was not explored, and thus disease-specific signals were likely missed.

With respect to glomerular disease subtypes other than LN, high rates of vascular events have been reported in non-ESRD populations with vasculitis,[68] membranous nephropathy,[17] IgA nephropathy,[70] and

the ApoL1 risk alleles associated with FSGS.[145] At the same time, both chronic kidney disease[133] and the nephrotic syndrome[7,146] have more generally been identified as strong cardiovascular risk factors. For example, age- and sex- standardized mortality rates in European dialysis patients compared with the general population were reported to be 11.0 (95% CI 10.6-11.4) for myocardial infarction, 8.4 (95% CI 8.0-8.8) for stroke, and 8.3 (95% CI 8.0-8.5) for other cardiovascular diseases.[147] In this same study, HR's for cardiovascular death by cause of ESRD (with ADPKD as the reference group) were also reported, albeit not as the primary focus of the manuscript, with findings consistent with those herein reported i.e. HR's in diabetic nephropathy of 4.1 (3.4–4.9) for MI and 3.5 (2.8–4.4) for stroke, and HRs in glomerulonephritis of 1.3 (1.1–1.7) for MI and 1.6 (1.3–2.1) for stroke. However, non-fatal events were not reported, analyses were only adjusted for 4 variables (age, sex, cause of kidney disease, and dialysis modality), baseline characteristics were not specifically compared across causes of ESRD, and all subtypes of glomerulonephritis were included together in a single disease group. Thus, our study expands upon these prior findings and translates them to a U.S. patient population.

There are a number of plausible hypotheses for our observed findings. The persistence of a particularly increased hazard for cardiovascular events even after adjustment for a prior history of diabetes among patients with diabetic nephropathy as a cause of ESRD likely speaks to the fact that development of severe nephropathy resulting in ESRD is a marker of prior poor diabetic control. We also suggest some hypotheses for why patients with IgAN or ADPKD had lower rates of cardiovascular events than those with other primary (FSGS, MN, MPGN) or secondary (LN, vasculitis) glomerular diseases. First, patients with IgAN or ADPKD do not typically develop the nephrotic syndrome (heavy proteinuria, hypoalbuminemia, and oedema), which itself results in hyperlipidaemia, increased thrombotic risk, and (through these mechanisms and others) heightened cardiovascular risk.[7,146,148] A prior history of nephrotic syndrome, or indeed continued nephrotic syndrome in those with residual urine output, might thus partly explain the relatively increased cardiovascular risk observed in those with FSGS, MN, or MPGN. Second, IgAN is less frequently treated with immunosuppressive therapies (and ADPKD is not treated with immunosuppressive therapies) when compared to other glomerular diseases.[115] Immunosuppressive medications can themselves induce elements of the metabolic syndrome (e.g. steroid or calcineurin-inhibitor associated diabetes or hypertension) and might contribute to the higher CV event rates observed in FSGS, MN, MPGN, LN, or vasculitis. Finally, systemic including direct vascular inflammation, as well as associated thrombotic disorders (e.g. anti-phospholipid syndrome) might partly explain the increased cardiovascular risk observed in patients with LN or vasculitis.[68,69]

Our study has some limitations. First, we included only patients who had survived long enough to develop ESRD. Whether similar differences exist in cardiovascular event rates across underlying causes of kidney disease in patients with earlier stages of kidney dysfunction could not be evaluated using this data source. Such an analysis is challenging to perform at any large-scale level in the U.S., given the absence of a national pre-ESRD glomerular disease registry, the rarity of glomerular disease subtypes at individual centres, and the non-specific nature of diagnosis codes for glomerular disease in administrative healthcare records. However, with the recent establishment of two large, NIH-funded, prospective glomerular disease cohort studies (Cure Glomerulonephropathy, CureGN,[2] and the Nephrotic Syndrome Study Network, NEPTUNE[1]), these barriers may soon be overcome. Second, without access to detailed clinical records or prescription data for most patients prior to dialysis initiation, we could not adjust for severity of pre-existing atherosclerotic disease (most patients lacked Medicare insurance prior to dialysis initiation and thus comorbidities were taken from physician-reported diagnoses on Medical Evidence Reports rather than from Medicare insurance claims), nor for other relevant factors such as baseline lipid values (only collected on Medical Evidence Reports since 2005 and missing in more than two thirds of patients even since then) or baseline medications (e.g. statins or medications blocking the renin-angiotensin-aldosterone system). Further, we could not explore the underlying pathogenic mechanisms contributing to differential risks across cause of ESRD groups, including the extent to which these differences are disease-related (e.g. history of thrombophilia or dyslipidaemia in patients with nephrotic syndrome or of systemic inflammation in patients with LN or vasculitis), treatment-related (e.g. corticosteroid-associated diabetes or calcineurin inhibitor-induced hypertension), or indeed related to the dialysis procedure itself (e.g. propensity for intra-dialytic hypotension or higher inter-dialytic weight gains). Laboratory data were missing in many patients and comorbidities were likely under-reported (e.g. only 89% of patients with diabetic nephropathy were reported to have diabetes mellitus),[149] factors that might have introduced bias or resulted in incomplete adjustment for confounding. Finally, although we studied prospectively collected data (i.e. Medical Evidence Reports, Medicare insurance claims, and Death Notifications collected “real time” shortly after events occur), these data were collected as part of routine clinical care and not with the specific objectives of this study in mind: thus, incomplete capture or misclassification of outcome events is possible.

Nevertheless, our study has several strengths. We examined a large, population-based, patient cohort and thus our study findings are broadly generalizable to most U.S. patients with ESRD due to glomerular disease, DN, or ADPKD. We were sufficiently powered to adjust for multiple potential confounders of

observed associations between cause of ESRD and cardiovascular and cerebrovascular events (e.g. patients with DN were older and predominantly male, whereas those with LN were younger and predominantly female, resulting in attenuation and exaggeration of effect estimates, respectively, after demographic adjustment), thus enabling us to identify independent, disease-specific, associations. We used advanced statistical techniques to optimize the internal validity of our findings, including use of multiple imputation to handle missing data, and comparison of sub-distribution and cause-specific Cox regression modelling approaches in an effort to better understand exposure-outcome associations.

In summary, we affirm high cardiovascular event rates in U.S. patients with ESRD treated with dialysis, confirming their appropriate classification as "very high risk" in cardiovascular disease prevention clinical guidelines.[150] Importantly, we have shown that relative hazards for cardiovascular events differ considerably by cause of ESRD. Although we cannot determine the exact underlying reasons for these differences, our data strongly support the presence of independent disease-specific influences. We advocate for the conduct of clinical studies that examine the impact of novel disease-specific interventions (e.g. control of systemic inflammation, prescription of less toxic immunosuppressive medications, more intensive control of nephrosis-associated hyperlipidaemia) on cardiovascular risk, as well as experiments that generate new knowledge regarding underlying disease biology. In the interim, we urge clinicians to actively consider and apply best practice cardiovascular guidelines[150] when treating dialysis patients, with the goal of eradicating disparities and improving outcomes.

6.6. Tables and figures (subsequent pages)

Table 1 (online only in published version). Baseline characteristics of U.S. patients with ESRD attributed to glomerular disease, diabetic nephropathy, or autosomal dominant polycystic kidney disease, who initiated haemodialysis or peritoneal dialysis in the U.S. 1997-2014*

	IgAN (N=9828)	FSGS N=(27029)	MN (N=5660)	MPGN (N=3718)	Lupus (N=12398)	Vasculitis (N=5023)	DN (N=567778)	ADPKD (N=26734)
Age, in years								
<40	3558 (36.2%)	7164 (26.5%)	702 (12.4%)	744 (20.0%)	6492 (52.4%)	457 (9.1%)	30345 (5.3%)	2121 (7.9%)
40-59	3955 (40.2%)	10343 (38.3%)	2058 (36.4%)	1573 (42.3%)	4361 (35.2%)	1409 (28.1%)	193431 (34.1%)	14650 (54.8%)
60-69	1209 (12.3%)	4487 (16.6%)	1260 (22.3%)	690 (18.6%)	937 (7.6%)	1230 (24.5%)	168682 (29.7%)	5219 (19.5%)
70+	1106 (11.3%)	5035 (18.6%)	1640 (29.0%)	711 (19.1%)	608 (4.9%)	1927 (38.4%)	175320 (30.9%)	4744 (17.7%)
Mean (std)	47.3 (16.3)	52.1 (17.3)	59.1 (15.5)	53.8 (16.7)	40.8 (15.0)	62.7 (15.8)	62.5 (12.9)	56.6 (12.9)
Median (IQR)	46.2 (34.2, 59.2)	52.2 (39.2, 65.2)	60.2 (48.2, 71.2)	54.2 (43.2, 66.2)	39.2 (28.2, 50.2)	65.2 (53.2, 74.2)	63.2 (54.2, 72.2)	55.2 (47.2, 65.2)
Gender								
Female	3276 (33.3%)	10232 (37.9%)	1929 (34.1%)	1480 (39.8%)	10113 (81.6%)	2288 (45.6%)	266684 (47.0%)	12310 (46.0%)
Male	6552 (66.7%)	16797 (62.1%)	3731 (65.9%)	2238 (60.2%)	2285 (18.4%)	2735 (54.4%)	301094 (53.0%)	14424 (54.0%)
Race								
White	7457 (75.9%)	15712 (58.1%)	3890 (68.7%)	2767 (74.4%)	5207 (42.0%)	4466 (88.9%)	370897 (65.3%)	21798 (81.5%)
Black	778 (7.9%)	10345 (38.3%)	1577 (27.9%)	745 (20.0%)	6479 (52.3%)	402 (8.0%)	164447 (29.0%)	4069 (15.2%)
Asian	1369 (13.9%)	709 (2.6%)	135 (2.4%)	147 (4.0%)	560 (4.5%)	78 (1.6%)	18995 (3.3%)	674 (2.5%)
Other	224 (2.3%)	263 (1.0%)	58 (1.0%)	59 (1.6%)	152 (1.2%)	77 (1.5%)	13439 (2.4%)	193 (0.7%)
Ethnicity								
Non-Hispanic	8585 (87.4%)	24794 (91.7%)	5160 (91.2%)	3331 (89.6%)	10491 (84.6%)	4561 (90.8%)	475114 (83.7%)	24406 (91.3%)
Hispanic	1191 (12.1%)	2103 (7.8%)	469 (8.3%)	363 (9.8%)	1844 (14.9%)	444 (8.8%)	90249 (15.9%)	2222 (8.3%)
Missing	52 (0.5%)	132 (0.5%)	31 (0.5%)	24 (0.6%)	63 (0.5%)	18 (0.4%)	2415 (0.4%)	106 (0.4%)
Region in the U.S.								
North-east	1919 (19.5%)	5384 (19.9%)	1176 (20.8%)	779 (21.0%)	2041 (16.5%)	932 (18.6%)	94173 (16.6%)	5364 (20.1%)
Mid-west	2285 (23.2%)	6346 (23.5%)	1360 (24.0%)	927 (24.9%)	2276 (18.4%)	1382 (27.5%)	122694 (21.6%)	6033 (22.6%)
South	3327 (33.9%)	11431 (42.3%)	2328 (41.1%)	1337 (36.0%)	5984 (48.3%)	1888 (37.6%)	249549 (44.0%)	10628 (39.8%)
West	2297 (23.4%)	3868 (14.3%)	796 (14.1%)	675 (18.2%)	2097 (16.9%)	821 (16.3%)	101362 (17.9%)	4709 (17.6%)
Dialysis modality								

Haemodialysis	7432 (75.6%)	21996 (81.4%)	4795 (84.7%)	3164 (85.1%)	10621 (85.7%)	4581 (91.2%)	519266 (91.5%)	21193 (79.3%)
Peritoneal dialysis	2396 (24.4%)	5033 (18.6%)	865 (15.3%)	554 (14.9%)	1777 (14.3%)	442 (8.8%)	48512 (8.5%)	5541 (20.7%)
Comorbidities								
Non-ambulant	89 (0.9%)	394 (1.5%)	124 (2.2%)	85 (2.3%)	242 (2.0%)	155 (3.1%)	34263 (6.0%)	294 (1.1%)
Atherosclerotic heart disease	730 (7.4%)	3297 (12.2%)	851 (15.0%)	400 (10.8%)	746 (6.0%)	598 (11.9%)	147576 (26.0%)	2709 (10.1%)
Cancer	302 (3.1%)	1378 (5.1%)	363 (6.4%)	208 (5.6%)	198 (1.6%)	277 (5.5%)	22369 (3.9%)	1028 (3.8%)
Congestive heart failure	932 (9.5%)	4019 (14.9%)	1087 (19.2%)	717 (19.3%)	1835 (14.8%)	776 (15.4%)	212681 (37.5%)	2453 (9.2%)
COPD	326 (3.3%)	1637 (6.1%)	440 (7.8%)	290 (7.8%)	302 (2.4%)	469 (9.3%)	44013 (7.8%)	1113 (4.2%)
Cerebrovascular disease	282 (2.9%)	1182 (4.4%)	334 (5.9%)	165 (4.4%)	645 (5.2%)	244 (4.9%)	59395 (10.5%)	1324 (5.0%)
Diabetes mellitus	1130 (11.5%)	4075 (15.1%)	908 (16.0%)	600 (16.1%)	1121 (9.0%)	904 (18.0%)	507149 (89.3%)	2412 (9.0%)
Hypertension	8372 (85.2%)	23018 (85.2%)	4743 (83.8%)	3130 (84.2%)	10011 (80.7%)	3720 (74.1%)	481047 (84.7%)	22751 (85.1%)
Previous or current smoking	569 (5.8%)	2168 (8.0%)	455 (8.0%)	379 (10.2%)	535 (4.3%)	226 (4.5%)	28075 (4.9%)	1902 (7.1%)
Peripheral vascular disease	308 (3.1%)	1381 (5.1%)	352 (6.2%)	201 (5.4%)	391 (3.2%)	325 (6.5%)	105305 (18.5%)	1023 (3.8%)
Missing	31 (0.3%)	75 (0.3%)	24 (0.4%)	11 (0.3%)	46 (0.4%)	9 (0.2%)	1705 (0.3%)	50 (0.2%)
BMI, Kg/m^2								
Underweight (<18.5)	242 (2.5%)	769 (2.8%)	142 (2.5%)	144 (3.9%)	684 (5.5%)	160 (3.2%)	11566 (2.0%)	793 (3.0%)
Normal (18.5-25)	3379 (34.4%)	7905 (29.2%)	1940 (34.3%)	1560 (42.0%)	5217 (42.1%)	2055 (40.9%)	145571 (25.6%)	9733 (36.4%)
Overweight (25-30)	2810 (28.6%)	7178 (26.6%)	1693 (29.9%)	1022 (27.5%)	3065 (24.7%)	1447 (28.8%)	159025 (28.0%)	7864 (29.4%)
Obese (>30)	3138 (31.9%)	10507 (38.9%)	1724 (30.5%)	865 (23.3%)	3083 (24.9%)	1268 (25.2%)	237678 (41.9%)	7555 (28.3%)
BMI, mean (std)	28.2 (7.3)	29.6 (8.4)	28.0 (7.1)	26.8 (7.0)	26.8 (7.5)	27.0 (6.9)	30.0 (7.9)	27.6 (7.0)
BMI, median (IQR)	26.8 (23.2, 31.8)	28.0 (23.7, 33.8)	26.6 (23.1, 31.4)	25.3 (22.0, 29.8)	25.2 (21.6, 30.1)	25.7 (22.5, 30.1)	28.7 (24.5, 34.2)	26.3 (22.9, 31.0)
Missing BMI	259 (2.6%)	670 (2.5%)	161 (2.8%)	127 (3.4%)	349 (2.8%)	93 (1.9%)	13938 (2.5%)	789 (3.0%)
Laboratory values								
eGFR, ml/min/1.73m^2								
Mean (std)	7.5 (3.7)	7.8 (3.8)	8.4 (4.2)	8.7 (4.5)	8.8 (4.5)	7.9 (4.0)	9.6 (4.4)	7.6 (3.4)
Median(IQR)	6.9 (5.0, 9.4)	7.1 (5.2, 9.7)	7.6 (5.4, 10.3)	7.8 (5.7, 10.8)	7.8 (5.6, 10.9)	7.2 (5.2, 9.8)	8.8 (6.5, 11.8)	7.0 (5.2, 9.4)
Missing	79 (0.8%)	254 (0.9%)	93 (1.6%)	53 (1.4%)	194 (1.6%)	41 (0.8%)	7192 (1.3%)	179 (0.7%)

Serum albumin, g/dL								
Mean(std)	3.4 (0.7)	3.3 (0.8)	2.8 (0.8)	2.9 (0.8)	2.9 (0.8)	3.0 (0.7)	3.1 (0.7)	3.7 (0.6)
Median (IQR)	3.5 (3.0, 3.9)	3.4 (2.8, 3.8)	2.9 (2.2, 3.5)	3.0 (2.4, 3.5)	2.9 (2.4, 3.5)	3.0 (2.5, 3.5)	3.1 (2.6, 3.5)	3.8 (3.4, 4.2)
Missing	2413 (24.6%)	6548 (24.2%)	1282 (22.7%)	859 (23.1%)	3002 (24.2%)	1217 (24.2%)	147884 (26.0%)	6676 (25.0%)
Haemoglobin, g/dL								
Mean(std)	9.9 (1.8)	10.0 (1.8)	9.9 (1.8)	9.8 (1.8)	9.3 (1.8)	9.6 (1.7)	9.8 (1.7)	10.4 (1.9)
Median(IQR)	9.9 (8.7, 11.1)	10.0 (8.9, 11.2)	9.9 (8.7, 11.0)	9.7 (8.6, 10.9)	9.3 (8.2, 10.4)	9.6 (8.5, 10.6)	9.7 (8.7, 10.8)	10.4 (9.2, 11.6)
Missing	1123 (11.4%)	3040 (11.2%)	614 (10.8%)	413 (11.1%)	1291 (10.4%)	528 (10.5%)	60771 (10.7%)	3124 (11.7%)
Neighbourhood-level socioeconomics								
% unemployment								
Mean (std)	7.6 (4.4)	8.3 (4.8)	8.0 (4.5)	7.7 (4.6)	8.9 (5.0)	7.7 (4.1)	8.7 (4.9)	7.5 (4.3)
Median (IQR)	6.8 (4.6, 9.6)	7.2 (4.8, 10.5)	7.0 (4.7, 10.1)	6.8 (4.5, 9.8)	8.0 (5.3, 11.5)	6.9 (4.8, 9.8)	7.8 (5.3, 11.1)	6.7 (4.5, 9.6)
Missing	18 (0.2%)	78 (0.3%)	14 (0.2%)	11 (0.3%)	29 (0.2%)	10 (0.2%)	1457 (0.3%)	71 (0.3%)
% below poverty								
Mean (std)	13.6 (8.9)	15.3 (9.9)	14.8 (9.5)	14.5 (9.5)	17.0 (10.2)	13.5 (8.7)	16.8 (10.2)	13.6 (8.9)
Median (IQR)	11.6 (6.8, 18.1)	13.2 (7.7, 20.8)	12.7 (7.4, 19.8)	12.3 (7.4, 19.3)	15.3 (8.8, 23.3)	11.8 (6.9, 18.1)	14.9 (8.9, 22.6)	11.8 (6.8, 18.3)
Missing	19 (0.2%)	79 (0.3%)	15 (0.3%)	10 (0.3%)	30 (0.2%)	10 (0.2%)	1433 (0.3%)	70 (0.3%)
% below high school								
Mean (std)	17.9 (11.1)	18.9 (10.9)	18.8 (10.8)	18.7 (10.7)	21.2 (11.9)	16.4 (10.0)	21.5 (12.3)	17.8 (10.8)
Median (IQR)	15.5 (9.7, 23.7)	17.0 (10.6, 25.2)	17.0 (10.7, 24.9)	16.7 (10.6, 24.8)	19.2 (12.0, 28.4)	14.2 (9.2, 21.3)	19.2 (12.2, 28.4)	15.7 (9.7, 23.6)
Missing	18 (0.2%)	71 (0.3%)	13 (0.2%)	10 (0.3%)	27 (0.2%)	10 (0.2%)	1352 (0.2%)	65 (0.2%)
Median rent, US$								
Mean (std)	725 (336)	684 (316)	673 (318)	666 (317)	699 (313)	725 (317)	671 (312)	696 (324)
Median (IQR)	684 (486, 911)	646 (447, 857)	633 (438, 840)	625 (431, 830)	657 (466, 869)	680 (516, 899)	631 (438, 842)	656 (464, 872)
Missing	77 (0.8%)	180 (0.7%)	39 (0.7%)	25 (0.7%)	62 (0.5%)	55 (1.1%)	4092 (0.7%)	200 (0.7%)
Median household income, US$								
Mean (std)	49646 (19431)	46284 (19108)	46366 (18742)	46090 (18072)	44535 (18224)	49783 (19198)	44200 (17814)	48722 (19435)
Median (IQR)	45807 (36208, 58907)	42106 (33181, 55010)	42102 (33629, 54771)	42598 (33880, 54495)	40722 (31791, 52766)	45649 (36450, 58831)	40452 (31913, 52251)	44545 (35437, 57629)

Missing	18 (0.2%)	77 (0.3%)	15 (0.3%)	11 (0.3%)	31 (0.3%)	11 (0.2%)	1478 (0.3%)	72 (0.3%)

*And remained on haemodialysis or peritoneal dialysis, with Medicare A&B as primary insurance, at study baseline (91 days after dialysis initiation). All values represent number (%) unless otherwise stated. IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Table 2. Cardiovascular event rates from 91 days to 5 years and 90 days after dialysis initiation, among U.S. patients with ESRD attributed to glomerular disease, diabetic nephropathy, or autosomal dominant polycystic kidney disease.

	% with event	Number of events	Years at risk	Event rate (per 100 person years)
Composite event (fatal or non-fatal cardiovascular event)				
IgAN	7.82	769	22895	3.36
FSGS	15.21	4111	71440	5.75
MN	19.08	1080	14671	7.36
MPGN	16.22	603	9311	6.48
LN	13.24	1641	33237	4.94
Vasculitis	17.02	855	11886	7.19
DN	33.19	188455	1314229	14.34
ADPKD	12.62	3375	69296	4.87
MI (fatal or non-fatal)				
IgAN	3.64	358	22970	1.56
FSGS	6.77	1830	71962	2.54
MN	8.89	503	14835	3.39
MPGN	6.67	248	9382	2.64
LN	5.19	644	33480	1.92
Vasculitis	7.21	362	11996	3.02
DN	15.19	86241	1341786	6.43
ADPKD	5.64	1509	69803	2.16
Stroke (fatal or non-fatal)				
IgAN	1.15	113	23176	0.49
FSGS	2.29	619	73002	0.85
MN	3.30	187	15093	1.24
MPGN	2.61	97	9531	1.02
LN	2.45	304	33771	0.90
Vasculitis	3.01	151	12200	1.24
DN	5.99	33994	1383828	2.46
ADPKD	2.47	660	70747	0.93
Any cardiovascular death				
IgAN	5.21	512	23265	2.20
FSGS	10.53	2846	73600	3.87
MN	12.70	719	15282	4.70
MPGN	11.03	410	9608	4.27
LN	9.05	1122	34041	3.30
Vasculitis	10.99	552	12318	4.48
DN	23.09	131091	1415715	9.26
ADPKD	8.28	2213	71315	3.10

IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

Table 3. Hazard ratios (95% confidence intervals) for cardiovascular events from 91 days to 5 years and 90 days after dialysis initiation, among U.S. patients with ESRD attributed to glomerular disease, diabetic nephropathy, or autosomal dominant polycystic kidney disease.

		Primary GN Subtypes			Secondary GN Subtypes		Non-GN Comparator Groups	
	IgAN	FSGS	MN	MPGN	LN	Vasculitis	DN	ADPKD
Composite event								
Model 1	ref	1.95	2.48	2.02	1.69	2.49	4.95	1.58
		(1.80-2.10)	(2.27-2.72)	(1.82-2.25)	(1.55-1.84)	(2.25-2.74)	(4.61-5.31)	(1.46-1.71)
Model 2	ref	1.72	1.84	1.70	2.09	1.63	3.53	1.24
		(1.59-1.85)	(1.68-2.02)	(1.53-1.89)	(1.92-2.28)	(1.48-1.80)	(3.29-3.78)	(1.15-1.34)
Model 3	ref	1.71	1.82	1.69	2.09	1.62	3.47	1.24
		(1.58-1.84)	(1.67-2.00)	(1.52-1.88)	(1.92-2.27)	(1.47-1.79)	(3.24-3.72)	(1.15-1.34)
Model 4	ref	1.68	1.79	1.65 (1.48-	1.97	1.61	3.13	1.25
		(1.56-1.81)	(1.63-1.96)	1.84)	(1.80-2.14)	(1.46-1.78)	(2.91-3.36)	(1.16-1.35)
Model 5	ref	1.65	1.67	1.55	1.86	1.55	2.97	1.29
		(1.53-1.78)	(1.52-1.83)	(1.40-1.73)	(1.71-2.03)	(1.41-1.71)	(2.77-3.20)	(1.19-1.39)
MI (fatal or non-fatal)								
Model 1	ref	1.82	2.39	1.75	1.39	2.11	4.34 (	1.50
		(1.62-2.03)	(2.09-2.74)	(1.49-2.05)	(1.22-1.58)	(1.82-2.44)	3.91-4.81)	(1.34-1.68)
Model 2	ref	1.66	1.93	1.54	1.63	1.56	3.40	1.26
		(1.48-1.86)	(1.68-2.20)	(1.31-1.81)	(1.44-1.86)	(1.35-1.80)	(3.06-3.77)	(1.12-1.41)
Model 3	ref	1.65	1.91	1.53	1.63	1.55	3.36	1.26
		(1.48-1.85)	(1.67-2.19)	(1.31-1.80)	(1.43-1.85)	(1.34-1.79)	(3.03-3.72)	(1.12-1.41)
Model 4	ref	1.62	1.88	1.50	1.57	1.57	3.06	1.25
		(1.44-1.81)	(1.64-2.16)	(1.27-1.76)	(1.38-1.79)	(1.36-1.82)	(2.75-3.40)	(1.12-1.41)
Model 5	ref	1.61	1.83	1.46	1.54	1.55	3.01	1.26
		(1.44-1.80)	(1.59-2.10)	(1.24-1.73)	(1.36-1.76)	(1.33-1.79)	(2.70-3.35)	(1.12-1.42)
Stroke (fatal or non-fatal)								
Model 1	ref	1.91	2.74	2.09	2.05	2.92	5.19	2.05
		(1.56-2.33)	(2.17-3.45)	(1.59-2.74)	(1.65-2.54)	(2.29-3.73)	(4.32-6.25)	(1.68-2.51)
Model 2	ref	1.70	2.20	1.81	1.96	2.11	3.75	1.67
		(1.39-2.08)	(1.74-2.78)	(1.38-2.38)	(1.58-2.43)	(1.65-2.69)	(3.12-4.51)	(1.36-2.03)

Model 3	ref	1.68	2.16	1.79	1.95	2.08	3.65	1.65
		(1.37-2.05)	(1.71-2.72)	(1.37-2.35)	(1.57-2.41)	(1.63-2.65)	(3.04-4.40)	(1.35-2.01)
Model 4	ref	1.73	2.17	1.84	1.94	2.11	3.54	1.65
		(1.41-2.12)	(1.71-2.76)	(1.40-2.42)	(1.55-2.41)	(1.64-2.71)	(2.92-4.29)	(1.35-2.03)
Model 5	ref	1.71	2.06	1.78	1.89	2.03	3.47	1.69
		(1.39-2.10)	(1.62-2.62)	(1.35-2.34)	(1.52-2.36)	(1.58-2.61)	(2.86-4.21)	(1.38-2.08)
Any CV death								
Model 1	ref	1.69	1.98	1.73	1.42	1.87	3.63	1.38
		(1.54-1.85)	(1.77-2.21)	(1.52-1.96)	(1.28-1.58)	(1.66-2.11)	(3.33-3.95)	(1.25-1.52)
Model 2	ref	1.56	1.55	1.51	1.93	1.32	2.86	1.15
		(1.42-1.71)	(1.39-1.73)	(1.33-1.71)	(1.74-2.14)	(1.17-1.48)	(2.63-3.12)	(1.05-1.26)
Model 3	ref	1.55	1.54	1.50	1.93	1.31	2.83	1.15
		(1.42-1.71)	(1.38-1.72)	(1.32-1.71)	(1.74-2.15)	(1.16-1.48)	(2.60-3.09)	(1.05-1.26)
Model 4	ref	1.54	1.51	1.47	1.81	1.30	2.57	1.16
		(1.40-1.69)	(1.35-1.69)	(1.29-1.67)	(1.63-2.01)	(1.15-1.47)	(2.35-2.81)	(1.06-1.28)
Model 5	ref	1.51	1.41	1.38	1.71	1.26	2.44	1.20
		(1.38-1.66)	(1.26-1.58)	(1.21-1.57)	(1.54-1.90)	(1.12-1.42)	(2.23-2.66)	(1.09-1.32)

All models were stratified by year of dialysis initiation and constructed as follows: Model 1 adjusted for cause of ESRD only; Model 2 additionally adjusted for demographic factors (age, sex, race, ethnicity), and geographic region; Model 3 additionally adjusted for socioeconomic factors; Model 4 additionally adjusted for comorbidities, dialysis modality, and BMI at time of dialysis initiation; Model 5 additionally adjusted for laboratory values reported at dialysis initiation. Global test to evaluate for violation of proportional hazards was non-significant for all outcomes (composite: p=0.0829; MI: p=0.1028; stroke: p=0.228; CV death: p=0.2182). IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

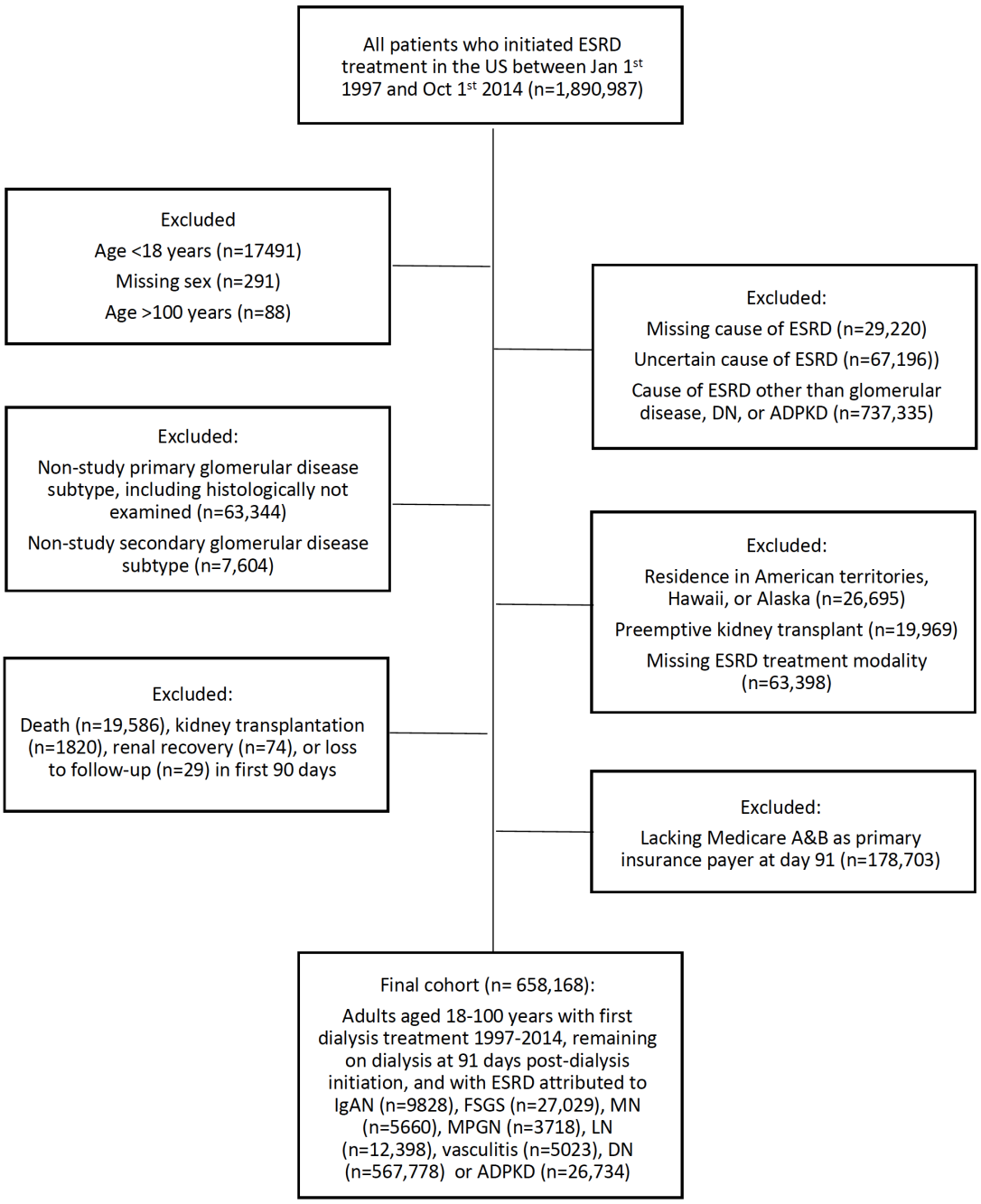

Figure 1. Assembly of the study cohort of 658,168 patients with ESRD attributed to any of 8 selected causes of ESRD who initiated and received at least 90 days of maintenance dialysis in the continental U.S., 1997-2014. ESRD, end-stage renal disease; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis.

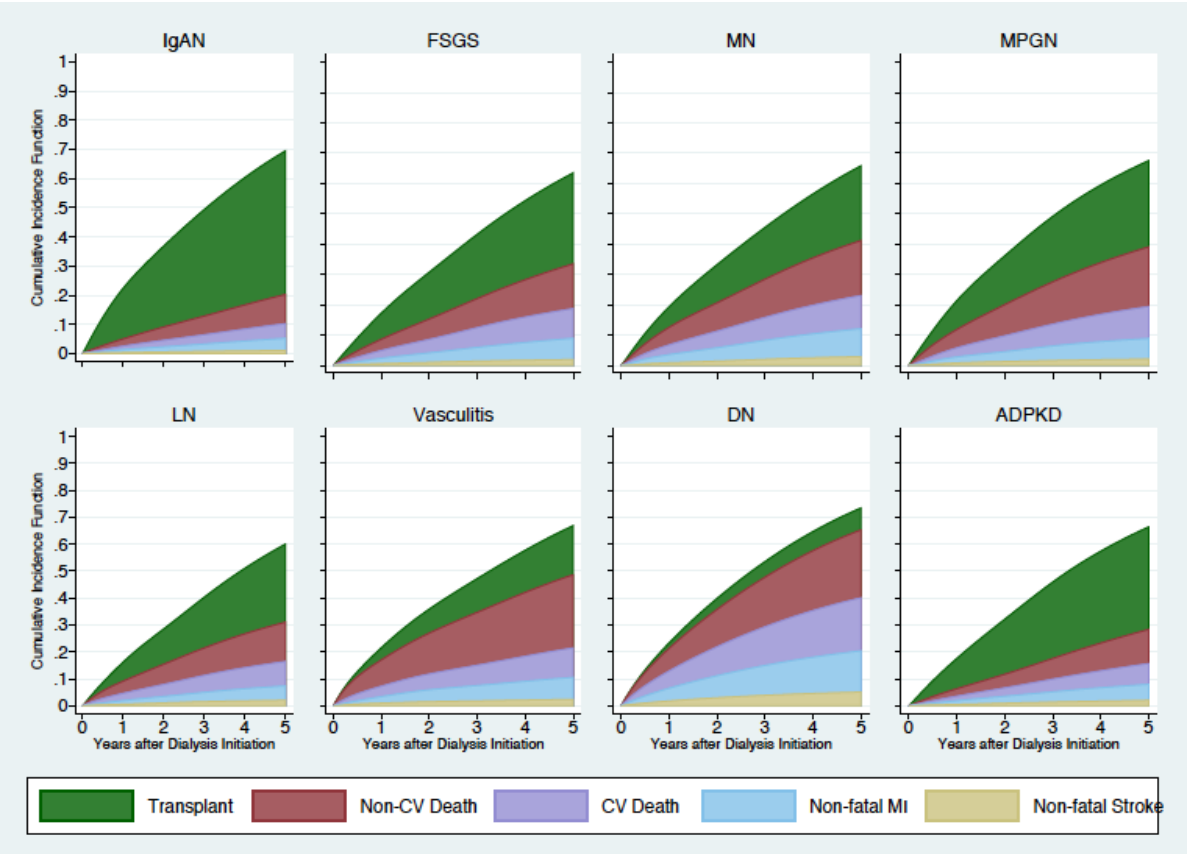

Figure 2. Cumulative incidence plots, stratified by cause of ESRD, showing 5-year cumulative incidences of first occurring cardiovascular or competing events among U.S. patients who initiated and received at least 90 days of dialysis for treatment of ESRD, 1997-2014. IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

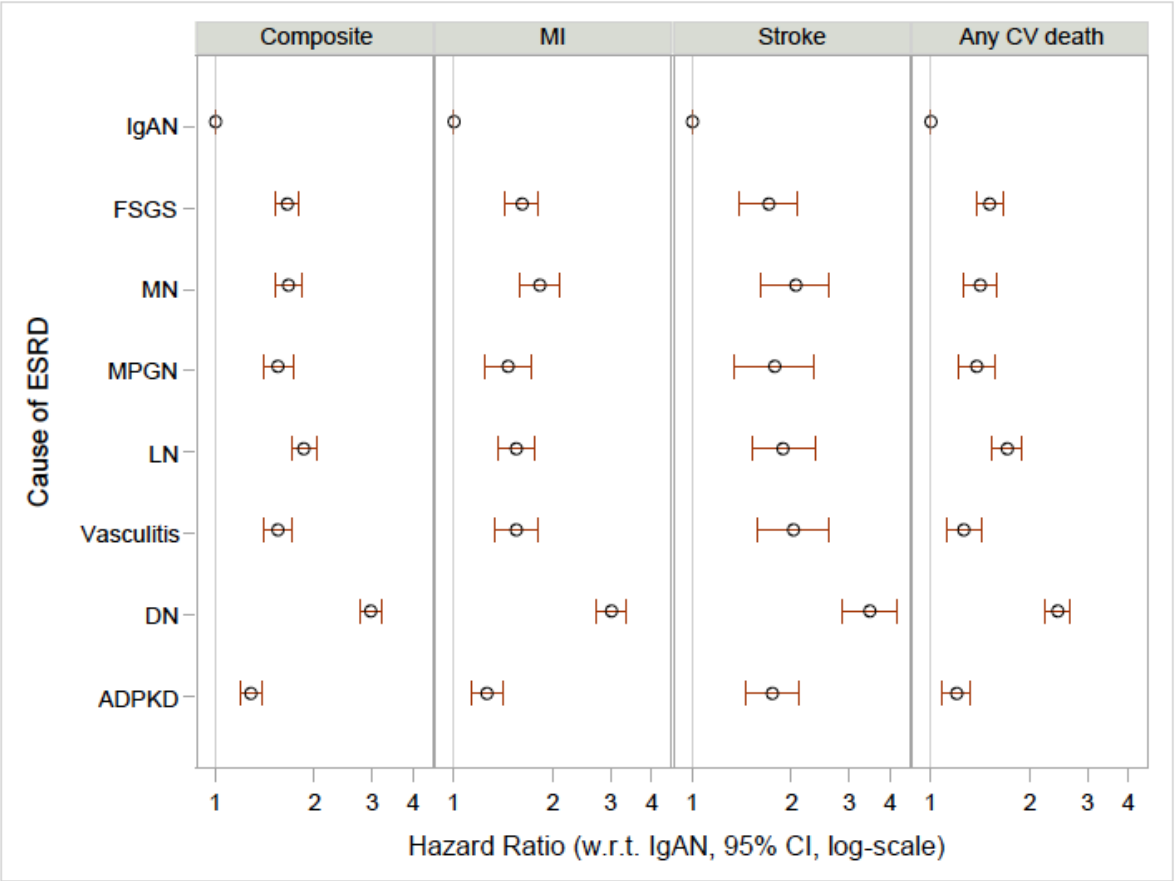

Figure 3: Sub-distribution hazard ratios with 95% confidence intervals from fully adjusted proportional hazards models for the primary cardiovascular outcome (MI, stroke, or cardiovascular death) and each of the major components of the composite outcome, showing relative hazards with respect to IgAN. The fully adjusted model was stratified by year of dialysis initiation and adjusted for cause of ESRD, demographic factors (age, sex, race, ethnicity), geographic region, socioeconomic factors, and baseline clinical factors at dialysis initiation (comorbidities, dialysis modality, BMI, laboratory values). MI, myocardial infarction; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

Chapter 7. Discussion and Conclusions

7.1. Chapter overview

This M.D. thesis closes major knowledge gaps regarding glomerular disease epidemiology, by determining international variation and temporal trends in glomerular disease frequency distributions, as well as by identifying associations between glomerular disease subtype and clinical outcomes in patients with end-stage kidney failure attributable to glomerular disease.

In this chapter, I will first describe how this body of research has advanced glomerular disease clinical research in general terms. Next, I will summarise novel research findings, impact, limitations, and lessons learned for each of the individual manuscripts presented in **Chapters 3 to 6**. Finally, I will discuss future research directions that were inspired by the work presented in this thesis.

7.2. General research contributions

As a whole, this body of work has demonstrated key findings with respect to the study of glomerular disease epidemiology.

The feasibility of international collaboration to study glomerular disease epidemiology

International collaboration is key to studying rare disease. It enables sufficient numbers of patients to be recruited to multisite clinical trials or observational cohort studies. Comparing differences in patient characteristics and outcomes across countries can uncover new knowledge and establish benchmarks. The International Kidney Biopsy Survey solicited responses from 29 centres across 18 countries, and successfully generated new knowledge regarding international glomerular disease epidemiology, confirming the feasibility and utility of international collaboration in this field.

The power of "big data" to study glomerular disease epidemiology

All four of the manuscripts presented in this thesis included over 20,000 patients with glomerular diseases. These numbers of patients are unprecedented in the existing glomerular disease literature. For the manuscripts using kidney biopsy diagnoses (**Chapters 3 and 4**), large patient numbers enabled multiple sub-group analyses to be performed, thus allowing the influence of race-ethnicity on observed geographic variation and temporal trends to be determined without loss of statistical power. For the manuscripts examining patients with end-stage kidney failure attributed to

glomerular disease enrolled in the USRDS (**Chapters 5 and 6**), the magnitude of the cohort enabled the application of multivariable regression techniques to explore the influence of confounding.

The importance of access to both histopathologic and clinical data to define and comprehensively characterise patient groups when studying glomerular disease epidemiology

While I discuss limitations of each of the individual studies within the manuscripts themselves, as well as in the sections below, I wish to highlight one unifying limitation particular to glomerular disease research here; that is, the need for a combination of histopathologic and clinical data to accurately diagnose and comprehensively characterise patients. Accordingly, for the first two studies presented in this thesis, examining kidney biopsy data, I was not in a position to further characterise histopathologically-defined disease entities based on clinical features e.g. to distinguish primary from cancer-associated membranous nephropathy, or determine whether cases of FSGS were accompanied by the nephrotic syndrome. Conversely, when studying USRDS data, I lacked access to histopathologic data and instead relied upon diagnoses assigned by treating nephrologists. A key focus of my future work will be to study glomerular disease epidemiology and clinical outcomes in population-level cohorts of patients with biopsy-confirmed glomerular disease for whom I also have access to comprehensive baseline and follow-up clinical and laboratory data.

7.3. Specific research contributions from individual manuscripts

Each of the manuscripts included in this thesis generated new knowledge, advanced my research skills, and is expected to have clinical, research, and public health impact. I also recognise that each of these manuscripts has certain limitations, which are also disclosed in the manuscripts themselves, and which will inform design the design of future studies aiming to overcome these limitations.

7.3.1 Glomerular disease frequencies by race, sex and region: results from the International Kidney Biopsy Survey

Study overview: This study examined variations in glomerular disease frequency distributions across 18 countries and 4 continents, using uniform approaches to case identification (i.e. all diagnoses identified in all consecutive kidney biopsies referred to the centre) and disease categorisation (i.e. adherence to standardised disease nomenclature provided by the study investigators).

New knowledge: This study confirmed significant international variation in glomerular disease frequency distributions across continents, confirming findings identified in prior national studies in a larger international study that adopted a standardised disease nomenclature. Specifically, diabetic

glomerulosclerosis (GS, 19.1%) and FSGS (19.1%) predominated in North America, lupus nephritis (38.1%) predominated in Latin America, and IgA nephropathy predominated in Europe (22.1%) and Asia (39.5%). A major new finding from this study – that included 42,603 glomerular disease diagnoses – was that FSGS and diabetic nephropathy were more frequent among Asian, Hispanic, or Caucasian patients living in the United States as compared to patients of similar ancestral origin living in Asia, Latin America, or Europe, respectively. For example, diabetic GS accounted for 17.4% of glomerular disease diagnoses among Latinos living in North America, *vs.* 4.3% among those living in Latin America ($p<0.001$). Corresponding figures for FSGS were 17.3% *vs.* 11.8%, respectively ($p<0.001$). These findings suggest that local environmental and lifestyle factors, and local biopsy policies, might influence glomerular disease epidemiology independently from race/ethnicity.

Impact: This study has been cited 53 times since its publication in 2018. One major impact of this study was confirming the feasibility of engaging multiple stakeholders from diverse geographic, economic, and cultural regions in a collaborative research effort. Since the publication of this paper additional international collaborative efforts to study glomerular disease epidemiology have emerged, including a recently founded European-wide glomerular disease registry coordinated by ERKNet,[3] as well as a very recently developed international registry capturing cases of COVD-19 in patients with glomerular disease.[151] In addition to demonstrating the potential for international collaboration, findings from this study are also hoped to have public health impact, by encouraging healthy living initiatives to prevent or reverse diabetes and obesity and, in doing so, modify glomerular disease risk. Finally, the figures and tables provided with this published report – including the online sharing of deidentified primary data – is expected to help clinicians formulating differential diagnoses and researchers determining the best international sites for clinical trials.

Limitations and lessons learned: One major limitation of the data source used to support this research was that summary demographics for each disease group, rather than individual patient level demographics, were submitted by each of the contributing centres. Nevertheless, by learning and applying appropriate statistical approaches, I was still able to extract meaningful findings from these data. Without knowing the size of the referral population, we could not calculate absolute incidence rates and instead calculated proportionate frequencies. Accordingly, we could not distinguish whether the higher frequency of diabetic GS and FSGS in North America represented a higher absolute frequency of these diagnoses, a lower absolute frequency of comparator diagnoses (e.g. IgA nephropathy or lupus nephritis), a higher likelihood to biopsy patients with morbidities such as diabetes or obesity, or a combination of these factors, in North America as compared to in other regions. Given that diabetic GS and obesity-related secondary forms of FSGS are heavily influenced

by lifestyle factors, and that the incidences of diabetes and obesity are steadily rising in the US,[75,76] we suspect that an absolute increase in the biopsy frequencies of diabetic GS and FSGS when patients migrate to North America is the most important contributor to this finding, representing a waning of the "healthy immigrant effect"[77,78].

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

Study overview: This study of 21,374 patients with biopsy-confirmed glomerular disease residing predominantly in the southeastern U.S. identified significant temporal trends in the relative kidney biopsy frequencies of many glomerular disease subtypes over three decades (1986-2015).

New knowledge: The most striking finding from this study was a marked increase in the renal biopsy frequency of diabetic glomerulosclerosis between 1986 and 2015, from 5.5% of cases in the earliest decade to 19.1% of cases most recently ($p<0.001$). This finding was consistently observed within all studied age, sex, and racial groups, with the exception of children. A second major finding was that the rising tide of FSGS observed in multiple U.S. studies at the end of the 20th century appeared to stabilise at the turn of the century, even among Black patients, in whom the risk was highest. Third, this study identified significant temporal trends even for the rarest of glomerular disease subtypes, highlighting the importance of large, representative, disease registries to study rare disease.

Impact: This manuscript was accompanied by an editorial when originally published in 2017 and has already had 59 citations. Our finding of an increasing frequency of diabetic glomerulosclerosis over the last 30 years is impactful from a public health perspective. In conjunction with findings from the IKBS study (**Chapter 3**), this finding highlights the importance of public health campaigns to prevent metabolic syndrome. Finally, the extensive tables and plots included in this publication, describing glomerular disease frequency distributions within demographic sub-groups, should serve as useful resources for clinicians formulating differential diagnoses or for investigators designing clinical trials.

Limitations and lessons learned: As was the case for the IKBS study, diagnoses reported in this study were largely histopathologically defined. However, all diagnoses were made by one of three experienced pathologists, and only after discussion with patients' treating nephrologists, thus giving opportunity to refine the diagnosis in light of clinical data. Informed by this approach, I aim to closely involve a nephropathologist when defining and categorising patients with glomerular disease diagnoses in future research studies, including when developing a local disease registry. Another limitation of this study, also shared by the IKBS study, was lack of knowledge of the referral

population size. Indeed, interpretation of our study is complicated by the steadily increasing number of biopsies referred to UNC over the study interval. While we report trends in proportional disease frequencies, we note that in some cases a decline in relative disease frequency was accompanied by an increase in the absolute number of diagnoses made. The underlying reasons for the rising background biopsy rate might include: a) a declining threshold to perform a kidney biopsy; b) an increasing referral population size, mirroring that occurring in North Carolina;[102,103] c) an increasing referral of biopsies to UNC over other centres; d) true increases in disease incidence. I recognise and discusses this limitation in the manuscript discussion section, and am careful to interpret my study findings with it in mind. This limitation also motivates the development of a national glomerular disease registry in Ireland, which would allow for calculation of population-level incidence rates.

7.3.3 Patient Characteristics and Outcomes by GN Subtype in ESRD

Study overview: In this study, I and my research team compared clinical characteristics at the time of renal replacement therapy initiation (dialysis or transplant), and subsequent mortality rates, in a national cohort of U.S. patients with treated end-stage kidney failure.

New knowledge: This was the first ever study to comprehensively characterise patients with kidney failure due to glomerular disease at the U.S. population level. I and my team identified major demographic and clinical differences across glomerular disease subtypes at the onset of kidney failure. For example, patients with end-stage kidney failure due to lupus nephritis had the highest proportion of young, Black, and female patients, while those with IgA nephropathy had the least comorbidities and were most likely to receive a kidney transplant or peritoneal dialysis (as opposed to haemodialysis) as their first renal replacement therapy modality. Further, we determined that mortality rates after the onset of kidney failure also differ considerably across glomerular disease subtypes, even after adjusting for demographic, socioeconomic, and clinical factors that might confound this association. Compared to IgAN, adjusted mortality hazards were significantly higher for all other glomerular disease subtypes, including: lupus nephritis (aHR=1.75, 95%CI 1.68-1.83), membranous nephropathy (aHR=1.23, 95%CI 1.17-1.29), FSGS (aHR=1.37, 95%CI 1.32-1.42), membranoproliferative GN (aHR=1.38, 95%CI 1.31-1.45), and vasculitis (aHR=1.51, 95%CI 1.45-1.58). The adjusted hazard for mortality in lupus nephritis was similar to in diabetic nephropathy (a typically poor prognostic group), while that in IgA nephropathy was lower than that in ADPKD (a typically good prognostic group). This heterogeneity across glomerular disease subtypes with respect to clinical characteristics and outcomes had not previously been reported in ESRD population.

Impact: This manuscript was accompanied by an editorial when originally published in 2015 and has already had 41 citations. To my eye, this study "broke the mould" with respect to research and public health reporting for glomerular diseases in the U.S. Our finding that glomerular disease subtype is strongly and significantly associated with mortality risk after the development of kidney failure challenged the prevailing public health and research reporting paradigm to lump glomerular diseases together in to a single disease category when reporting clinical outcomes in patients with end-stage kidney failure. The importance of, and interest in, this finding is evidenced by the fact that multiple papers (including five more from this author[137,152-155]) have since been published examining glomerular disease subtype as a predictor of clinical outcomes in patients with and without kidney failure.[156-158] Findings from this paper are also clinically relevant: they can inform the counselling of patients with glomerular disease approaching kidney failure regarding their expected clinical course following dialysis initiation and how it might compare to that of patients with other kidney diseases.

Limitations and lessons learned: This work represented my first venture in to using "big data" to study glomerular disease epidemiology. I learned to appreciate the strengths of population-level research approaches, including an ability to report absolute disease incidence and outcome event rates, as well as the generalisability of study findings to real-world populations. However, the absence of comprehensive laboratory and medication data in the USRDS precluded my ability to tease apart potential mechanisms for the identified mortality differences across glomerular disease subtypes, such as differences in disease activity or in exposure to immunosuppressive or nephrotoxic medications. Accordingly, in my future research efforts, I aim to link cohorts of patients with glomerular disease to more comprehensive electronic healthcare record data, akin to the model incorporated in the National Registry of Rare Kidney Diseases (RaDaR) in the United Kingdom.[159]

7.3.4 Cause of kidney disease and cardiovascular events in a national cohort of US patients with end-stage renal disease on dialysis: a retrospective analysis

Study overview: Again using USRDS data, this study examined differences in baseline characteristics and cardiovascular outcomes (through linkage to Medicare insurance claims data) across causes of kidney failure in a national cohort of U.S. patients who initiated dialysis between 1997 and 2014.

New knowledge: After identifying mortality differences across glomerular disease subtypes in patients with end-stage kidney failure (**Chapter 5**), the present study (**Chapter 6**) added granularity to this finding by describing differences in fatal and non-fatal cardiovascular event rates across glomerular disease subtypes, again at the U.S. population-level. We identified significant between-group differences in cardiovascular outcomes after dialysis initiation according to cause of kidney

failure. For example, in a cumulative incidence model including first events, by 5 years and 90 days after dialysis initiation, 49.3% of patients with IgAN had received a kidney transplant, 10.3% had experienced a fatal or non-fatal cardiovascular event, and 10.0% had died from a non-cardiovascular cause. In contrast, only 8.1% of patients with diabetic nephropathy had received a kidney transplant, while 40.1% had experienced a cardiovascular event and 25.2% a non-cardiovascular death. Significant differences across glomerular disease subtypes persisted even after adjusting for demographic, socioeconomic, and other clinical differences, again demonstrating that the adjusted hazard for adverse outcomes was highest for lupus nephritis and lowest for IgA nephropathy.

Impact: This manuscript was accompanied by an editorial and selected as an "Editor's Choice" manuscript when originally published in 2019 and has been cited 14 times since then. Clinically, this manuscript can be used to counsel patients regarding their absolute and relative risks for cardiovascular events following dialysis initiation. Findings from this study also generate hypotheses regarding pathologic factors linking glomerular disease subtype to cardiovascular risk, that can be explored in future observational and interventional studies e.g. studying the influence of medications (immunosuppressive agents, aspirin, or statins) on cardiovascular risk. Finally, findings from this study highlight the importance of considering cause of kidney failure when designing studies and reporting clinical outcomes in patients with end-stage kidney failure more generally.

Limitations and lessons learned: In this second study using data from the USRDS, I further advanced my research skills by learning to analyse insurance claims data to capture cardiovascular events. A limitation of this approach is that I could not validate whether administrative codes accurately and completely capture cardiovascular events specifically in patients with glomerular disease. Further, medication data could not be included in this analyses, as not all patients with end-stage kidney failure have Medicare Part D (medication cover) insurance or use this cover to purchase all of their medications.[160] Accordingly, when designing future clinical outcomes studies in patients with glomerular disease, I will aim to collect comprehensive, time-updated, medication data.

7.4. Next Directions

Largely inspired and guided by the works presented in this thesis, as well as my ongoing contribution to multi-centre collaborative glomerular disease research networks (Cure Glomerulonephropathy, CureGN,[2] and the Nephrotic Syndrome Study Network, NEPTUNE[1]), my next career step is to develop a glomerular disease registry at Cork University Hospital. I ultimately aim to expand this registry nationally, and internationally, to support population-level audit and research.

Population-level disease registries represent an ideal solution to studying glomerular disease epidemiology, by enabling the determination of absolute disease incidence and outcome event rates (by knowing the denominator population size), as well as producing nationally generalisable findings.

However, the establishment and maintenance of population-level registries is logistically and financially challenging. Additionally, as a research platform, registries are somewhat inflexible, as data are restricted to the fields specified in the study protocol. Finally, without a guaranteed funding stream, many registries are unsustainable in the longer term. Other solutions must therefore be identified, to supplement and complement these manual data collection efforts.

Accordingly, informed by the work presented in this thesis, and additional work I more recently conducted using electronic healthcare data to study glomerular diseases (not presented in this thesis),[22,23] the registry I am actively developing will incorporate the following features:

- Kidney biopsy data will be collected for all patients, in view of the integral role of histopathology in defining and characterising glomerular diseases
- Once Ireland launches its planned universal healthcare record[161], I aim to automatically import laboratory, medication, and other clinical data collected at the time of routine healthcare encounters, akin to the RaDaR model adopted in the United Kingdom[159]
- I will aim to expand a local registry at Cork University Hospital nationally, and to ensure that this registry is interoperable with international efforts, to enable multinational studies
- I will apply natural language processing to extract information from kidney biopsy reports to support specific studies e.g. to identify patients with certain histologic features of interest
- The registry will act as a platform to supports trials-within-a-study, to minimise duplication of data collection efforts and allow registry and trial funding streams to support one another

7.5. Concluding Statement

To conclude, in this body of work, I have demonstrated the feasibility and utility of using large-scale kidney pathology and clinical research datasets to uncover new knowledge regarding glomerular disease epidemiology. I propose that secondary data analysis and data linkage approaches can also be used to support glomerular disease registries, observational studies, and clinical trials, with the

goal of offering all patients with rare glomerular diseases an opportunity to share their data and participate in research, culminating in new knowledge discovery and enhanced patient outcomes.

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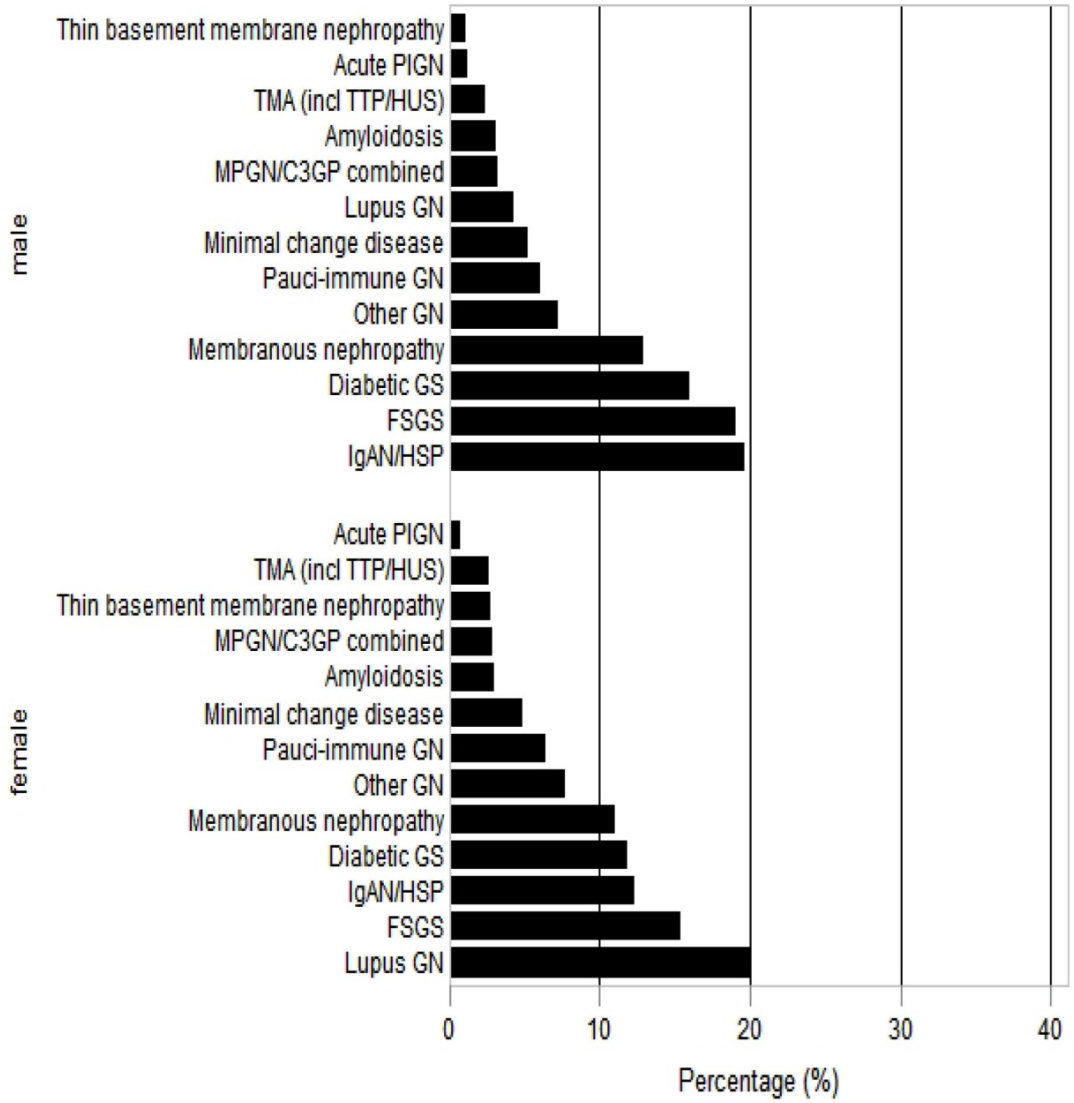
Appendix 1: Supplemental materials for Manuscript 1 (Chapter 3)



Supplemental Figure 1. Glomerular Disease Subtype Kidney Biopsy Frequencies, by sex. GN, glomerulonephritis; NOS, not otherwise specified; TMA, thrombotic microangiopathic anemia; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; GBM, glomerular basement membrane; MPGN, membranoproliferative GN; C3GP, C3 glomerulopathy; FSGS, focal and segmental glomeruloslcerosis; GS, glomerulosclerosis; MIDD, monoclonal immune deposition diseases; IgAN, IgA nephropathy; HSP, Henoch Schonlein purpura; PIGN, post-infectious GN. "Other GN" includes diagnoses with less than 100 cases overall (diffuse mesangial sclerosis, Finnish type congenital nephrotic syndrome, immunotactoid glomerulopathy, collagenofibrotic glomerulopathy, fibronectin glomerulopathy, IgM nephropathy, polyarteritis nodosa, preeclampsia/eclampsia, Fabry disease, lipoprotein glomerulopathy, sickle cell glomerulopathy).

Appendix A: Letter of invitation to participate in the survey

Dear ERA-EDTA Immunonephrology Working Group Member,

You are invited to contribute data to a survey of the frequency of categories of medical renal disease that are diagnosed by renal biopsy. The International Kidney Biopsy Survey is a collaborative effort between the ASN Glomerular Disease Advisory Group (GDAG), the Renal Pathology Society, and the Immunonephrology Working Group of the European Renal Association-European Dialysis and Transplant Association.

IKBS will not ask for any patient identifiers or other protected health information.
The short term goal of the IKBS is to establish the incidence of pathologic categories of disease in native kidney biopsy specimens. These data also will be used to estimate the numbers of patients with the various categories of glomerular disease who would be potential recruits into clinical trials and other research endeavours.

The long term goal of this IKBS is to use this process as an early small step toward establishing a national and international glomerular disease registries of individual patients with linked diagnoses, robust clinical data and possibly biorepository samples. However, the deidentified data in this current survey will have no direct links to current or future patient registries containing protected health information.

We have completed the first attempt to gather survey data by requesting data form the members of the Renal Pathology Society. Some of the data we received (limited to glomerular diseases) is provided on the attached page. These data have not been verified or evaluated with respect to sampling bias at specialty institutions.

International Kidney Biopsy Survey (IKBS) Instructions

Important: The source of data for this survey must be all consecutive native kidney biopsies processed by a nephropathology laboratory during a specified time interval. The data must not be derived from clinical databases of selected patients seen by individual nephrologists or groups of nephrologists, or from registries that contain selected categories of disease.
Each nephropathology laboratory should submit only one survey.

Nephropathology Dataset Information:

Primary respondent name:

Corresponding respondent name if different from above:

Corresponding respondent phone number:

Corresponding respondent email address:

Names of other contributors:

Contributing institution(s) with address(s):

Dataset interval in years (one year or longer):

Dataset start date:

Dataset end date:

Estimated source-population size (see explanation below):*

*If you can make a reasonable estimate, what is your estimate of the population size from which your biopsy diagnoses were obtained. For example, if you estimate that you receive specimens from approximately one third of the renal biopsies performed in a geographical region that has a population of 9 million, you would record an estimate of 3 million as the population size from which your data are derived. If you are not able to make a reasonable estimate (e.g. because your specimens come from many different locations with many different nephropathology services dividing the specimens), record “NA” (not available). These data will allow calculation of the biopsy diagnosis incidence (e.g. 10 IgA nephropathy renal biopsy diagnoses per million population per year).

Diagnostic Category Frequency Data

For each specified category of disease, please record the total number of specimens with the diagnosis for the specified interval using the most recent time interval that is available for submission.

When there are multiple hierarchical subcategory for a category of disease, please feel free to complete data only for the most general category if you do not have ready access to the subcategory data. For example, provide only the total number of FSGS or lupus nephritis cases if you do not have data on the numbers of subsets within these categories. The required major categories are highlighted blue in the survey Excel spreadsheet.

Only use “0” for a diagnosis that you looked for but did not identify during the survey interval (e.g. record “0” for collagenofibrotic glomerulopathy if you did not make this diagnosis during the observation period).

If you do not use a category or do not keep a record of a category, record “NA” (not available) rather than “0” for this category. For example use NA for tip lesion variant of FSGS or for C1q nephropathy if these are categories that are not separately recorded in your data.

If a specimen has more than one diagnosis, each diagnosis (i.e. all diagnoses) should be included in the survey. For example, if one specimen has diagnoses of diabetic glomerulosclerosis, anti-GBM disease and acute tubulointerstitial nephritis, all three diagnoses should be included in your totals.

Patient Demographic Data

If demographic data are available to you for each diagnostic category, record the mean age and age range, number of males vs females, and number with known race/ethnicity (white, black, Asian, Latino, other, or unknown). However, please provide only the diagnostic category data if you do not have ready access to the demographic data.

Appendix B: Demographic characteristics for all reported kidney disease diagnoses, by geographic region: see Microsoft Excel spreadsheet, available online

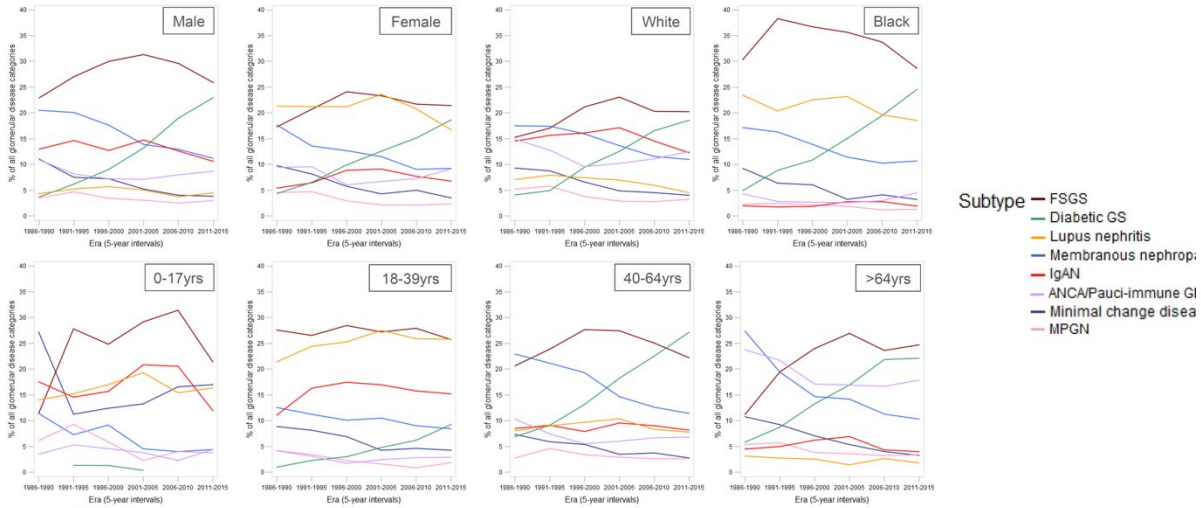
https://oup.silverchair-cdn.com/oup/backfile/Content_public/Journal/ndt/33/4/10.1093_ndt_gfx189/5/gfx189_ikbs_supplemental_appendix_b_-_final.xlsx?Expires=1611664618&Signature=vCGC~Vktm1HTNoR16E8gcsHemLchE9AQj2v3FbK2YEI~vs9EUmiP-kvbMP4OZyyDC0zztF6KawK6HlWK535DN3w0OLQdV9zuV~tHyM-uWxV5AHqbNw1E1skx~XPOGLmtGGjPxfZXSVkbllEg7RoUFCUrnZEDAaCDeqBn~UgqyRn1WBuvtwnAc6AKpiHASBkpNpsnUpkDov~d98aTSnaSoc2q2knqDX4NqVLR1WATKLUt2-yT2qyJFFo3EhtslAShVq7KdO67stmcL1Vy6aGLxn-T9jWa-RG8iETbzu4g21szzoc22rXPZSNBcqz6HVQChfIo6c7i-VqSZa7Icz5xA__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA

Appendix 2: Supplemental materials for Manuscript 2 (Chapter 4)

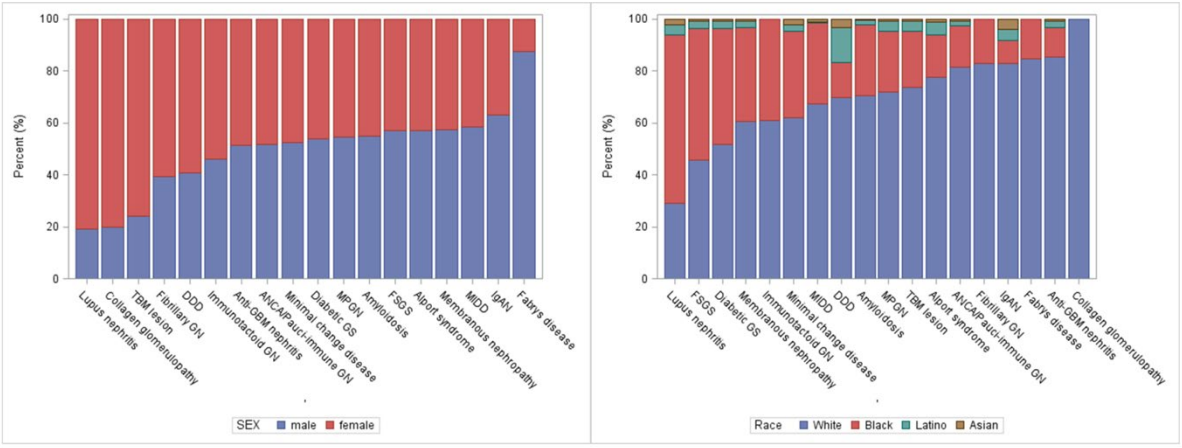
Supplemental Table 1: Temporal trends in region of origin of all kidney biopsy samples with known region of origin* referred to UNC nephropathology 1986-2015.

Region, n (%)	1986-1995 n=4937	1996-2005 n=13,823	2006-2015 n=17,932	Total n= 36,692	p-value
North Carolina	3583 (72.6)	7234 (52.3)	9137 (51.0)	19,954 (54.4)	<0.001
Other Southeastern U.S. State	1225 (24.8)	6120 (44.3)	8263 (46.1)	15,608 (42.5)	<0.001
Non-Southeastern U.S. State	127 (2.6)	331 (2.4)	482 (2.7)	940 (2.6)	0.30
Country outside of the U.S.	<10 (<1)	138 (1.0)	50 (0.3)	190 (0.5)	0.05

* Missing region of origin declined from 25% in 1986-1995, to 5% in 1996-2005, to 0.3% in 2006-2015.



Supplemental Figure S1. Temporal trends in the relative renal biopsy frequencies of the most common glomerular disease subtypes, by patients age, sex, and race. Percentages represent proportions among all studied glomerular disease subtypes in the designated demographic subgroup. FSGS, focal segmental glomeruloslcerosis; GS, glomerulosclerosis; IgAN, IgA nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis



Supplemental Figure S2. Sex and race distributions within each of the 18 studied glomerular disease subtypes. TBM, thin basement membrane lesion; GN, glomerulonephritis; MPGN, membranoproliferative GN (non-DDD); DDD, dense deposit disease; GBM, glomerular basement membrane; ANCA, anti-neutrophil cytoplasmic antibody; GS, glomerulosclerosis; FSGS, focal segmental glomerulosclerosis; MIDD, monoclonal immune deposition disease; IgAN, IgA nephropathy.

Appendix 3: Supplemental materials for Manuscript 3 (Chapter 5)

Table S1: Unadjusted and adjusted mortality hazard ratios for mortality by method of analysis (complete-case vs. missing data imputed)

	ADPKD	IgAN	MN	FSGS	MPGN	Vasculitis	LN	DN
Model 1								
Complete case	1.63	1.0	2.65	2.14	2.48	4.32	2.17	5.60
	(1.55-1.71)	(referent)	(2.49-2.81)	(2.04-2.25)	(2.32-2.65)	(4.09-4.57)	(2.06-2.29)	(5.35-5.86)
8 Imputed data sets	1.59	1.0	2.59	2.03	2.37	4.15	2.12	5.48
	(1.53-1.66)	(referent)	(2.46-2.72)	(1.95-2.12)	(2.25-2.51)	(3.96-4.35)	(2.03-2.21)	(5.28-5.68)
15 imputed data sets	1.59	1.0	2.59	2.03	2.37	4.15	2.12	5.48
	(1.53-1.66)	(referent)	(2.46-2.72)	(1.95-2.12)	(2.25-2.51)	(3.96-4.35)	(2.03-2.21)	(5.28-5.68)
Model 2								
Complete case	1.10	1.0	1.71	1.76	1.95	2.31	2.72	3.35
	(1.05-1.16)	(referent)	(1.61-1.82)	(1.67-1.84)	(1.83-2.08)	(2.18-2.45)	(2.58-2.87)	(3.20-3.50)
8 Imputed data sets	1.08	1.0	1.69	1.69	1.87	2.23	2.72	3.29
	(1.04-1.12)	(referent)	(1.61-1.78)	(1.63-1.76)	(1.77-1.97)	(2.13-2.33)	(2.61-2.85)	(3.17-3.41)
15 imputed data sets	1.08	1.0	1.69	1.69	1.87	2.23	2.72	3.29
	(1.04-1.12)	(referent)	(1.61-1.78)	(1.63-1.76)	(1.77-1.97)	(2.13-2.33)	(2.61-2.85)	(3.17-3.41)
Model 3								
Complete case	1.24	1.0	1.40	1.64	1.63	1.99	2.26	2.59
	(1.18-1.30)	(referent)	(1.32-1.49)	(1.56-1.72)	(1.52-1.74)	(1.88-2.11)	(2.15-2.39)	(2.47-2.71)
8 Imputed data sets	1.22	1.0	1.40	1.58	1.56	1.96	2.27	2.24
	(1.17-1.27)	(referent)	(1.33-1.47)	(1.52-1.65)	(1.48-1.65)	(1.87-2.06)	(2.17-2.38)	(2.15-2.32)
15 imputed data sets	1.22	1.0	1.40	1.58	1.56	1.96	2.27	2.24
	(1.17-1.27)	(referent)	(1.33-1.47)	(1.52-1.65)	(1.48-1.65)	(1.87-2.06)	(2.17-2.38)	(2.15-2.32)
Model 4								
Complete case	1.22	1.0	1.21	1.39	1.41	1.50	1.71	1.99
	(1.17-1.28)	(referent)	(1.14-1.28)	(1.33-1.46)	(1.33-1.50)	(1.42-1.58)	(1.63-1.80)	(1.90-2.08)
8 Imputed data sets	1.23	1.0	1.23	1.37	1.38	1.51	1.75	1.73
	(1.18-1.27)	(referent)	(1.17-1.29)	(1.32-1.42)	(1.31-1.45)	(1.45-1.58)	(1.68-1.83)	(1.67-1.79)
15 imputed data sets	1.22	1.0	1.23	1.37	1.38	1.51	1.75	1.73
	(1.18-1.27)	(referent)	(1.17-1.29)	(1.32-1.42)	(1.31-1.45)	(1.45-1.58)	(1.68-1.83)	(1.67-1.79)

All values are HR (95% CI). **Model 1: unadjusted; model 2: demographic adjusted; model 3: demographic and comorbidity adjusted; model 4: demographic, comorbidity and ESRD therapy modality adjusted.** Complete case analysis includes only patients with complete information (n=575,032). Multiple imputation analysis uses the entire patient sample (n=840,574) and imputes missing data using a joint modelling approach, generating k datasets that are analysed separately. Results are then combined. The final log HR equals the mean of the individual log HRs for each dataset. Standard error (SE) is computed taking into account uncertainty deriving from both the sampled values and the imputation process. ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; LN, lupus nephritis, DN; diabetes related ESRD.

Table S2: Cause-specific mortality

Cause of Death	**ADPKD**	**IgAN**	**MN**	**FSGS**	**MPGN**	**Vasculitis**	**LN**	**DN**
Total deaths, n	12,053	2,839	3,382	13,721	2,405	4,686	6,741	485,481
Cardiovascular, n (%)	5,158 (42.8)	1,099 (38.7)	1,465 (43.3)	6,123 (44.6)	907 (37.7)	1,604 (34.2)	2,835 (42.1)	238,820 (49.2)
Infection-related, n (%)	1,182 (9.8)	282 (9.9)	306 (9.1)	1,357 (9.9)	254 (10.6)	543 (11.6)	942 (14.0)	53,888 (11.1)
Malignancy-related, n (%)	754 (6.3)	171 (6.0)	221 (6.5)	654 (4.8)	145 (6.0)	197 (4.2)	154 (2.3)	11,575 (2.4)
Other, n (%)	3,012 (25.0)	775 (27.3)	828 (24.5)	3,377 (24.6)	677 (28.2)	1,355 (28.9)	1,540 (22.9)	99,470 (20.5)
Missing, n (%)	1,947 (16.2)	512 (18.0)	562 (16.6)	2,210 (16.1)	422 (17.6)	987 (21.1)	1,270 (18.8)	81,728 (16.8)

ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetes related ESRD.

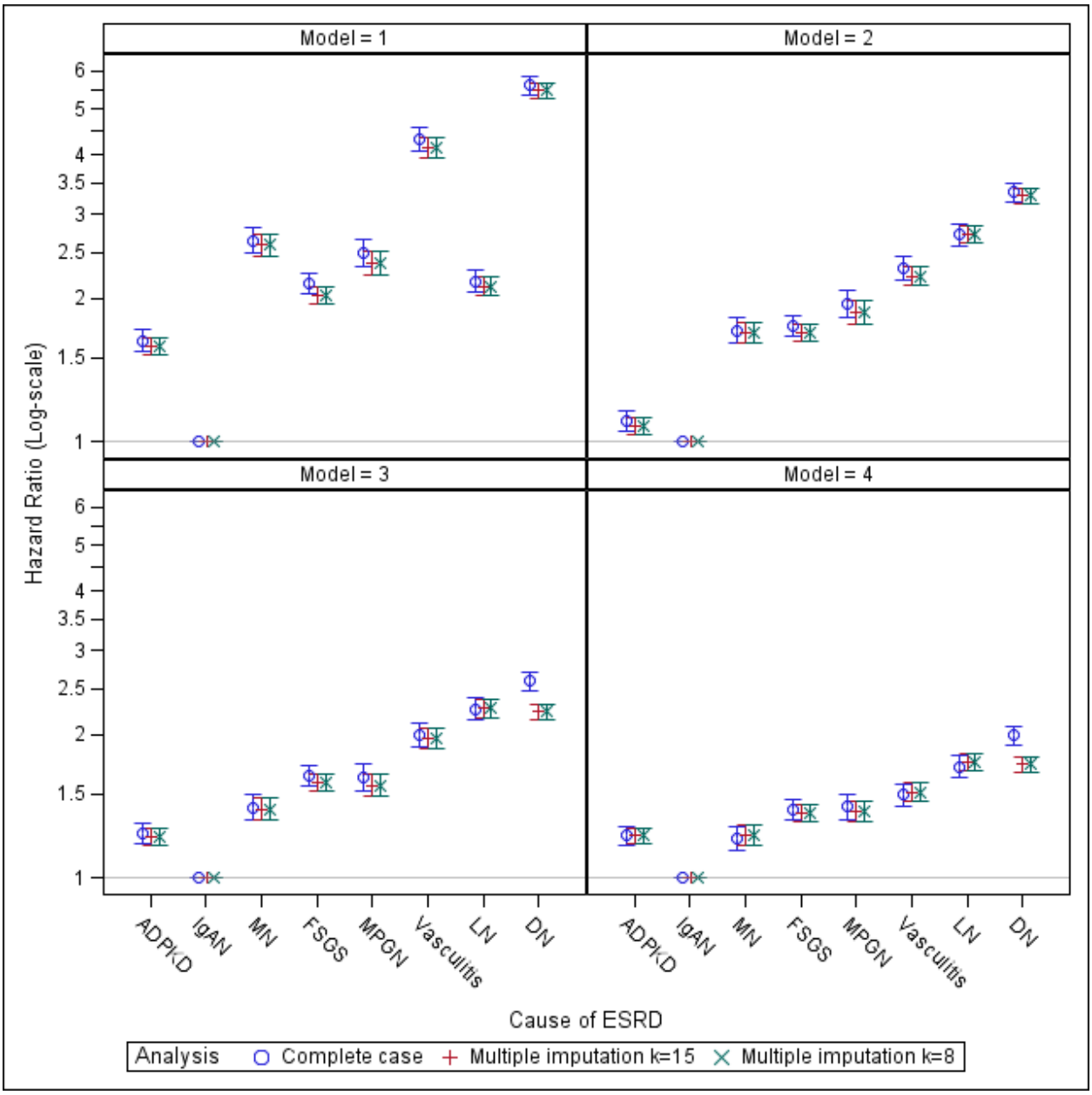


Figure S1: Unadjusted and adjusted mortality hazard ratios by method of analysis stratified by model. **Model 1: unadjusted; model 2: demographic adjusted; model 3: demographic and comorbidity adjusted; model 4: demographic, comorbidity and ESRD therapy modality adjusted.** Complete case analysis includes only patients with complete information (n=575,032). Multiple imputation analysis uses the entire patient sample (n=840,574) and imputes missing data using a joint modelling approach, generating k datasets that are analysed separately. Results are then combined. The final log HR equals the mean of the individual log HRs for each dataset. Standard error (SE) is computed taking into account uncertainty deriving from both the sampled values and the imputation process. ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetes related ESRD.

Cause of ESRD diagnostic codes:

- Focal and segmental glomerulosclerosis (FSGS): 582.1
- IgA nephropathy (IgAN): 583.81
- Membranous nephropathy (MN): 583.1
- Membranoproliferative glomerulonephritis (MPGN): 583.21, 583.22
- Lupus nephritis: 710.0
- Vasculitis: 446.4, 446.20
- Diabetes mellitus (DM): 250.40, 250.41
- Autosomal-dominant polycystic kidney disease (ADPKD): 753.13

ESRD therapy modality categories:

- Haemodialysis: home, dialysis facility, long-term care facility haemodialysis
- Peritoneal dialysis: continuous ambulatory and continuous cycling peritoneal dialysis
- Kidney transplantation: deceased donor and living donor kidney transplantation, including combined organ transplantations. Incident (baseline) ESRD modality defined as pre-emptive kidney transplant when transplant date and date of ESRD therapy initiation coincide.

Cause of death categories:

- **Cardiac:** Myocardial infarction, acute (23); Pericarditis, incl. Cardiac tamponade (25); Atherosclerotic heart disease (26); Cardiomyopathy (27); Cardiac arrhythmia (28); Cardiac arrest, cause unknown (29); Valvular heart disease (30); Pulmonary oedema due to exogenous fluid (31); Congestive Heart Failure (32).
- **Vascular:** Pulmonary embolus (35); Cerebrovascular accident including intracranial haemorrhage (36); Ischemic brain damage/Anoxic encephalopathy (37); Haemorrhage from transplant site (38); Haemorrhage from vascular access (39); Haemorrhage from dialysis circuit (40); Haemorrhage from ruptured vascular aneurysm (41); Haemorrhage from surgery (not 38, 39, or 41) (42); Other haemorrhage (not 38-42, 72) (43); Mesenteric infarction/ischemic bowel (44).
- **Cardiovascular:** Cardiac and Vascular causes combined
- **Infection:** Septicaemia due to internal vascular access (33); Septicaemia due to vascular access catheter (34); Peritoneal access infectious complication, bacterial (45); Peritoneal access infectious complication, fungal (46); Peritonitis (complication of peritoneal dialysis) (47); Central nervous system infection (brain abscess, meningitis, encephalitis, etc.) (48); Septicaemia due to peripheral vascular disease, gangrene (51); Septicaemia, other (52); Cardiac infection (endocarditis) (61); Pulmonary infection (pneumonia, influenza) (62); Abdominal infection (peritonitis (not comp of PD), perforated bowel, diverticular disease, gallbladder) (63); Genito-urinary infection (urinary tract infection, pyelonephritis, renal abscess) (70).
- **Malignancy-related:** Malignant disease, patient ever on Immunosuppressive therapy (82); Malignant disease (not 82) (83).

Appendix 4: Supplemental materials for Manuscript 4 (Chapter 6)

Supplemental Table 1. Five-year cumulative incidences of cardiovascular, cerebrovascular, or competing events (kidney transplantation, non-cardiovascular death), from 91 days to 5 years and 90 days after dialysis initiation, among U.S. patients initiating dialysis 1997-2014

	Primary GN Subtypes				Secondary GN Subtypes		Non-GN Comparator Groups	
	IgAN	**FSGS**	**MN**	**MPGN**	**LN**	**Vasculitis**	**DN**	**ADPKD**
Kidney transplantation, %	49.3	30.0	24.6	28.5	29.0	18.2	8.1	38.1
Non-CV death, %	10.0	14.7	18.1	19.6	14.6	27.2	25.2	12.7
Any CV event, %	10.3	18.7	23.0	19.4	16.6	21.5	40.1	16.3
CV death, %	5.1	9.8	10.9	10.5	9.1	11.0	19.7	7.7
Non-fatal MI, %	4.2	7.0	9.2	6.8	5.4	8.1	15.3	6.0
Non-fatal stroke, %	1.0	1.9	2.9	2.1	2.1	2.4	5.1	2.0

IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; MI, myocardial infarction.

Supplemental Table 2. Hazard ratios (95% confidence intervals) for cardiovascular events from 91 days to 5 years and 90 days after dialysis initiation, *with death or kidney transplantation treated as censoring rather than competing events (sensitivity analysis),* in U.S. patients with ESRD attributed to one of 6 glomerular diseases, diabetic nephropathy, or autosomal dominant polycystic kidney disease.

		Primary GN Subtypes			Secondary GN Subtypes		Non-GN Comparator Groups	
	IgAN	FSGS	MN	MPGN	LN	Vasculitis	DN	ADPKD
Composite event								
Model 1	ref	1.69 (1.56-1.82)	2.16 (1.97-2.37)	1.86 (1.67-2.07)	1.44 (1.32-1.57)	2.25 (2.04-2.48)	4.26 (3.97-4.57)	1.43 (1.32-1.55)
Model 2	ref	1.50 (1.39-1.62)	1.55 (1.42-1.70)	1.51 (1.36-1.68)	2.02 (1.85-2.19)	1.39 (1.26-1.53)	3.06 (2.86-3.28)	1.09 (1.01-1.18)
Model 3	ref	1.49 (1.38-1.61)	1.54 (1.41-1.69)	1.51 (1.35-1.68)	2.02 (1.85-2.20)	1.38 (1.25-1.52)	3.03 (2.82-3.25)	1.09 (1.01-1.18)
Model 4	ref	1.48 (1.37-1.60)	1.51 (1.38-1.66)	1.45 (1.30-1.62)	1.87 (1.71-2.04)	1.36 (1.23-1.50)	2.76 (2.56-2.97)	1.10 (1.01-1.19)
Model 5	ref	1.44 (1.33-1.56)	1.36 (1.24-1.49)	1.32 (1.18-1.47)	1.72 (1.58-1.88)	1.28 (1.16-1.41)	2.57 (2.39-2.76)	1.15 (1.06-1.25)
MI (hospitalized or fatal)								
Model 1	ref	1.61 (1.43-1.80)	2.14 (1.87-2.46)	1.65 (1.40-1.94)	1.21 (1.06-1.38)	1.99 (1.72-2.31)	4.11 (3.70-4.56)	1.37 (1.22-1.54)
Model 2	ref	1.45 (1.30-1.62)	1.60 (1.40-1.83)	1.37 (1.17-1.61)	1.66 (1.46-1.89)	1.30 (1.12-1.50)	3.08 (2.78-3.42)	1.07 (0.96-1.20)
Model 3	ref	1.45 (1.29-1.62)	1.59 (1.39-1.82)	1.37 (1.16-1.61)	1.66 (1.46-1.89)	1.29 (1.12-1.49)	3.05 (2.75-3.39)	1.07 (0.96-1.20)
Model 4	ref	1.43 (1.27-1.60)	1.57 (1.37-1.80)	1.31 (1.11-1.55)	1.56 (1.36-1.77)	1.30 (1.12-1.51)	2.78 (2.50-3.10)	1.07 (0.95-1.21)
Model 5	ref	1.40 (1.25-1.57)	1.45 (1.27-1.67)	1.23 (1.04-1.45)	1.48 (1.29-1.68)	1.24 (1.07-1.44)	2.65 (2.38-2.95)	1.10 (0.98-1.24)
Stroke (hospitalized or fatal)								
Model 1	ref	1.70 (1.39-2.08)	2.48 (1.97-3.14)	1.97 (1.51-2.59)	1.79 (1.44-2.22)	2.76 (2.17-3.53)	5.02 (4.17-6.04)	1.87 (1.53-2.28)
Model 2	ref	1.49 (1.22-1.82)	1.83 (1.45-2.31)	1.61 (1.23-2.11)	2.00 (1.61-2.47)	1.75 (1.37-2.23)	3.43 (2.85-4.13)	1.41 (1.15-1.72)
Model 3	ref	1.48 (1.21-1.81)	1.81 (1.43-2.28)	1.60 (1.22-2.09)	2.00 (1.61-2.48)	1.73 (1.35-2.20)	3.36 (2.79-4.04)	1.40 (1.15-1.71)
Model 4	ref	1.53 (1.25-1.88)	1.82 (1.43-2.31)	1.62 (1.23-2.13)	1.92 (1.54-2.40)	1.74 (1.36-2.24)	3.25 (2.69-3.94)	1.41 (1.14-1.72)
Model 5	ref	1.50	1.63	1.49	1.81	1.62	3.09	1.48

		(1.22-1.84)	(1.28-2.08)	(1.13-1.96)	(1.45-2.26)	(1.26-2.08)	(2.55-3.74)	(1.20-1.81)
CV death								
Model 1	ref	1.72	2.09	1.86	1.45	2.15	4.19	1.38
		(1.56-1.89)	(1.86-2.34)	(1.63-2.12)	(1.31-1.61)	(1.91-2.43)	(3.84-4.57)	(1.25-1.52)
Model 2	ref	1.52	1.48	1.50	2.19	1.31	3.02	1.05
		(1.39-1.67)	(1.32-1.66)	(1.32-1.71)	(1.97-2.43)	(1.16-1.48)	(2.77-3.29)	(0.96-1.16)
Model 3	ref	1.52	1.47	1.50	2.20	1.30	2.99	1.05
		(1.38-1.67)	(1.31-1.64)	(1.32-1.71)	(1.98-2.44)	(1.15-1.47)	(2.74-3.26)	(0.95-1.16)
Model 4	ref	1.50	1.44	1.44	2.02	1.27	2.69	1.06
		(1.36-1.65)	(1.28-1.61)	(1.26-1.64)	(1.81-2.24)	(1.13-1.44)	(2.46-2.95)	(0.96-1.17)
Model 5	ref	1.46	1.27	1.29	1.84	1.19	2.49	1.13
		(1.33-1.61)	(1.13-1.42)	(1.13-1.47)	(1.66-2.05)	(1.05-1.34)	(2.27-2.72)	(1.02-1.24)

All models were stratified by year of dialysis initiation and constructed as follows: Model 1 adjusted for cause of ESRD only; Model 2 additionally adjusted for demographic factors (age, sex, race, ethnicity) and geographic region; Model 3 additionally adjusted for socioeconomic factors; Model 4 additionally adjusted for comorbidities, dialysis modality, and BMI at time of dialysis initiation; Model 5 additionally adjusted for laboratory values reported at dialysis initiation. IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

Supplemental Table 3. Hazard ratios (95% confidence intervals) for cardiovascular events from 91 days to 5 years and 90 days after dialysis initiation, with death or kidney transplantation treated as competing events, in U.S. patients with ESRD attributed to one of 6 glomerular diseases, diabetic nephropathy, or autosomal dominant polycystic kidney disease, *complete case sensitivity analysis (n=446,381)*

		Primary GN Subtypes			Secondary GN Subtypes		Non-GN Comparator Groups	
	IgAN	FSGS	MN	MPGN	LN	Vasculitis	DN	ADPKD
Composite event								
Model 1	ref	1.94 (1.77-2.13)	2.40 (2.15-2.68)	1.99 (1.75-2.26)	1.64 (1.48-1.82)	2.47 (2.20-2.78)	4.86 (4.47-5.30)	1.53 (1.40-1.69)
Model 2	ref	1.70 (1.56-1.87)	1.77 (1.59-1.98)	1.67 (1.47-1.90)	2.04 (1.84-2.26)	1.62 (1.45-1.83)	3.47 (3.19-3.77)	1.21 (1.10-1.33)
Model 3	ref	1.69 (1.55-1.86)	1.76 (1.57-1.96)	1.66 (1.46-1.89)	2.03 (1.84-2.25)	1.61 (1.44-1.81)	3.41 (3.14-3.71)	1.21 (1.10-1.32)
Model 4	ref	1.67 (1.53-1.83)	1.73 (1.55-1.93)	1.62 (1.42-1.83)	1.91 (1.73-2.12)	1.61 (1.43-1.81)	3.05 (2.80-3.33)	1.23 (1.12-1.35)
Model 5	ref	1.64 (1.49-1.79)	1.60 (1.43-1.79)	1.51 (1.33-1.71)	1.81 (1.63-2.00)	1.54 (1.37-1.72)	2.89 (2.66-3.15)	1.27 (1.15-1.39)
MI (hospitalized or fatal)								
Model 1	ref	1.81 (1.58-2.08)	2.32 (1.97-2.73)	1.68 (1.38-2.04)	1.36 (1.16-1.58)	2.23 (1.88-2.65)	4.29 (3.79-4.86)	1.44 (1.26-1.66)
Model 2	ref	1.65 (1.44-1.89)	1.86 (1.58-2.19)	1.48 (1.22-1.80)	1.60 (1.37-1.87)	1.65 (1.39-1.96)	3.37 (2.97-3.81)	1.22 (1.06-1.40)
Model 3	ref	1.65 (1.44-1.88)	1.85 (1.57-2.18)	1.48 (1.21-1.79)	1.60 (1.37-1.86)	1.65 (1.39-1.96)	3.33 (2.94-3.77)	1.21 (1.06-1.39)
Model 4	ref	1.62 (1.41-1.85)	1.82 (1.55-2.14)	1.46 (1.20-1.77)	1.54 (1.31-1.79)	1.66 (1.40-1.98)	3.00 (2.64-3.41)	1.23 (1.07-1.41)
Model 5	ref	1.61 (1.41-1.84)	1.77 (1.50-2.08)	1.42 (1.17-1.73)	1.51 (1.29-1.76)	1.63 (1.37-1.94)	2.94 (2.59-3.34)	1.24 (1.08-1.42)
Stroke (hospitalized or fatal)								
Model 1	ref	2.14 (1.67-2.74)	3.01 (2.26-3.99)	2.33 (1.68-3.23)	2.23 (1.71-2.90)	3.09 (2.30-4.17)	5.42 (4.31-6.82)	2.20 (1.72-2.82)
Model 2	ref	1.90 (1.48-2.43)	2.41 (1.81-3.20)	2.03 (1.46-2.81)	2.13 (1.63-2.77)	2.24 (1.66-3.02)	3.91 (3.11-4.93)	1.79 (1.40-2.30)
Model 3	ref	1.88 (1.47-2.40)	2.37 (1.78-3.14)	2.00 (1.44-2.78)	2.12 (1.62-2.76)	2.21 (1.64-2.98)	3.82 (3.03-4.81)	1.78 (1.39-2.28)
Model 4	ref	1.88 (1.47-2.41)	2.36 (1.77-3.13)	1.97 (1.42-2.74)	2.05 (1.57-2.67)	2.22 (1.65-3.00)	3.66 (2.90-4.62)	1.76 (1.37-2.25)
		1.86	2.22	1.89	2.00	2.12	3.57	1.81

		(1.45-2.38)	(1.67-2.95)	(1.36-2.62)	(1.53-2.60)	(1.57-2.86)	(2.83-4.51)	(1.41-2.32)
CV death								
Model 1	ref	1.73	1.93	1.68	1.41	1.85	3.66	1.37
		(1.54-1.94)	(1.68-2.22)	(1.43-1.97)	(1.24-1.60)	(1.60-2.14)	(3.29-4.06)	(1.22-1.54)
Model 2	ref	1.58	1.50	1.45	1.90	1.29	2.86	1.14
		(1.41-1.77)	(1.31-1.72)	(1.24-1.70)	(1.67-2.15)	(1.12-1.50)	(2.57-3.17)	(1.01-1.28)
Model 3	ref	1.57	1.49	1.45	1.90	1.29	2.83	1.13
		(1.41-1.76)	(1.30-1.71)	(1.24-1.70)	(1.67-2.15)	(1.11-1.49)	(2.55-3.14)	(1.01-1.27)
Model 4	ref	1.56	1.47	1.41	1.78	1.28	2.57	1.16
		(1.40-1.75)	(1.28-1.69)	(1.20-1.65)	(1.57-2.02)	(1.11-1.48)	(2.31-2.85)	(1.03-1.30)
Model 5	ref	1.53	1.36	1.30	1.67	1.23	2.42	1.20
		(1.37-1.71)	(1.18-1.56)	(1.11-1.52)	(1.48-1.90)	(1.06-1.42)	(2.18-2.69)	(1.07-1.34)

All models were stratified by year of dialysis initiation and constructed as follows: Model 1 adjusted for cause of ESRD only; Model 2 additionally adjusted for demographic factors (age, sex, race, ethnicity) and geographic region; Model 3 additionally adjusted for socioeconomic factors; Model 4 additionally adjusted for comorbidities, dialysis modality, and BMI at time of dialysis initiation; Model 5 additionally adjusted for laboratory values reported at dialysis initiation. IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease.

Appendix 5: Published manuscripts