24-year trends in incidence and mortality of nephrotic syndrome – a population-based cohort study

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Sub-Saharan Africa, unrelated to the work in this paper. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Abstract

Introduction

Nephrotic syndrome is a renal disorder characterized by severe proteinuria and hypoalbuminemia, caused by primary glomerular diseases or secondary to systemic conditions.[1,2] Recent data describing the incidence and mortality of nephrotic syndrome in adults are sparse. During the past decades, the global occurrence of conditions associated with secondary nephrotic syndrome such as diabetes and cancer have increased proportionally with population ageing.[3,4] This may have influenced the incidence of nephrotic syndrome. In the same period, numerous factors could have affected the mortality of nephrotic syndrome. On the one hand, the general global increased burden of non-communicable disease combined with an ageing population may have changed patient composition of first-time nephrotic syndrome patients.[5-7] On the other hand, treatment of selected forms of primary nephrotic syndrome has improved with the introduction of new therapy regimens including biologics[8,9] which, together with improved treatment and prevention of cardiovascular complications, may have decreased the mortality of nephrotic syndrome.[10,11]

While not all patients with nephrotic syndrome have a kidney biopsy, previous studies on incidence and mortality of nephrotic syndrome have focused on patients with kidney biopsies.[12-29] These studies report incidence of adult nephrotic syndrome between 0.58 and 4.2 per 100,000 person-years,[12-21] and overall mortality of 6-21% during up to five years follow-up after nephrotic syndrome.[21-23] Additionally, several studies have examined the mortality of nephrotic syndrome in subgroups of patients with specific types of glomerulopathy.[24-29] As previous studies have focused on the subset of nephrotic syndrome patients with a kidney biopsy, the overall incidence and mortality of nephrotic syndrome remains unclarified.

We used the Danish medical databases to address this knowledge gap. We examined: 1) the age- and sex-specific incidence and mortality of nephrotic syndrome, 2) the changes in the incidence and mortality of nephrotic syndrome in adults from 1995 through 2018, and 3) patient characteristics including histopathological findings in kidney biopsies in patients with nephrotic syndrome over time and by age group.

Methods

Setting and study design

We conducted this cohort study using routinely collected medical data from universally tax-funded hospitals including all providers of specialized nephrology care in Denmark.[30] Personal civil registration numbers enabled linkage of data from administrative and medical databases on an individual level.[31]

Nephrotic syndrome

We identified all adults (≥18 years) with a first-time recorded nephrotic syndrome diagnosis in Danish hospitals during 1995-2018. Primary or secondary discharge diagnoses in inpatients, outpatients or emergency rooms visitors were included. Nephrotic syndrome diagnoses were obtained from the Danish National Patient Registry with information on every inpatient hospital contact since 1977, and every outpatient clinic or emergency room contact since 1995, using International Classification of Diseases 8th revision (ICD-8) before 1994 and ICD-10 thereafter.[32] The first date of the contact was defined as index date, and only patients without prior nephrotic syndrome diagnoses or a prior kidney transplant were included. Data on adults at risk of nephrotic syndrome in Denmark (~4.6 million adult population) were obtained from Statistics Denmark,[33,34] assuming that each adult person alive at 1 January each year from 1995 through 2018 contributed with one person-year.[35]

Mortality

Information on all-cause mortality was obtained from the Danish Civil Registration System,[31] and data on the cause of death was obtained from the Danish Register of Causes of Death (including ICD-10 diagnoses since 1994).[36]

Covariates

Sex and age were obtained from the Danish Civil Registration System.[31] Prior kidney diagnoses (i.e. glomerulonephritis [excl. nephrotic syndrome], renal tubulointerstitial diseases, acute kidney injury or chronic kidney disease, hypertensive nephropathy, diabetic nephropathy) and comorbidities (i.e. diabetes, liver disease, chronic pulmonary disease, any connective tissue disease, congestive heart failure, and

thromboembolic disease) recorded up to 10 years prior to the index date were obtained from the Danish National Patient Registry (see codebooks in eAppendices).[32] Information on non-hematological and hematological cancers were obtained by combining the Danish National Patient Registry and the Danish Cancer Registry, which contains ICD-10 diagnoses since 1978 (reporting being mandatory since 1987) on cancer diagnoses in Denmark.[37] Information on concurrent pregnancy at the index date was obtained from the Danish National Patient Registry.[32]

The histopathological diagnoses from kidney biopsies performed within +/- 180 days of the nephrotic syndrome index date was acquired from the Danish National Pathology Registry with complete nationwide coverage from 1999, but with first the kidney biopsies recordings from selected hospitals beginning in 1972.[38] Every patient with a kidney biopsy was categorized based on the type of histopathology in the biopsy closest to the index date and categorized as: membranous nephropathy, membranoproliferative glomerulonephritis, other proliferative glomerulonephritis (mesangioproliferative glomerulopathy, proliferative endocapillary glomerulonephritis, or unspecified proliferative glomerulonephritis), focal segmental glomerulosclerosis, diabetic nephropathy, minimal change disease, other glomerulonephritis (deposition glomerulonephritis, necrotizing and crescentic glomerulonephritis and vasculitis, or unspecified glomerulonephritis), or non-glomerular conditions (see codebook in eAppendices).

Statistical analyses

Patient characteristics

We tabulated patient characteristics at index date including sex, median age with interquartile range [IQR], age group, place of diagnosis (emergency room, inpatient, or outpatient), proportions with specific comorbidities during the prior 10 years, ongoing pregnancy, and kidney biopsies within +/- 180 days from index date.

Incidence

We computed both crude and standardized incidence rates of recorded nephrotic syndrome to evaluate changes in incidence of nephrotic syndrome over time, accounting for the increasing age of the Danish

population. We divided number of first-time nephrotic syndrome events by person-time, to estimate incidence of first-time nephrotic syndrome events per 100,000 person-years with 95% confidence intervals (CI) overall, and by sex, age, and calendar period (1995-2000, 2001-2006, 2007-2012, 2013-2018).[35] Direct standardized incidence rates with 95% CIs were computed weighting the crude incidence rates by age and sex distributions in Denmark in year 2000.[39]

Mortality

We followed the patients from index date until death, emigration, or 1 January 2020 whatever occurred first. We computed and plotted direct standardized mortality rates of nephrotic syndrome per 100 person-years by calendar period and age group, internally weighted by sex and age group in the nephrotic syndrome cohort. The absolute 1- and 5-year risk of death after nephrotic syndrome was estimated by 1-Kaplan-Meier estimates with 95% CIs. We used a Cox proportional hazards analysis to compute hazard ratios (HRs) with 95% CIs of death both crude, and adjusted for age, sex, calendar year of diagnosis, and any prior comorbidity (diabetes, liver disease, pulmonary disease, connective tissue disease, congestive heart failure, thromboembolic disease, non-hematological cancer, and hematological cancer) by calendar period (with 1995-2000 as reference) and age group (with 50-59 years as reference). The assumption of proportionality was confirmed by inspection of log-log plots and plots of Schoenfeld residuals. Further, we computed 1-year mortality and HR of death in patients with a comorbidity during the 10 years prior to the nephrotic syndrome index date using patients without each type of comorbidity as reference. Among the patients who died after an nephrotic syndrome diagnosis during 1995-2018, we calculated the proportion of deaths attributed to diseases grouped by ICD-10 chapter.

Pathology

Among patients with a biopsy, we calculated and plotted the proportion of patients with each type of pathology by calendar period and age group. Moreover, we estimated the 1- and 5-year mortality and HRs of death by type of pathology compared with patients with membranous nephropathy. For this analysis,

the follow-up started at the nephrotic syndrome index date or the date of kidney biopsy, whichever came last. Patients with a recorded biopsy date after the date of death (13 of 2,060 patients) were excluded.

Additional analyses

We restricted our main study period to 1995-2018 as outpatient data were not available in the Danish National Patient Registry before 1995. To explore the trends in the epidemiology of adult nephrotic syndrome before 1995, we repeated the analyses of the standardized incidence and mortality rates of nephrotic syndrome including data from 1979 through 2018 from the same data sources as in the main analyses.

All analyses were conducted in R version 4.0.4 (R Core Team, 2021, www.r-project.org).[40-44]

The study was reported to the Danish Data Protection Agency (record number 2015-57-0002) by Aarhus University (record number 2016-051-000001/812). According to Danish legislation approval from an ethics committee or informed consent from patients is not required for registry-based studies.

Results

Patient characteristics

We identified 3,970 patients with first-time recorded nephrotic syndrome during 1995-2018 (eFigure 1). In total, 57% of patients were men, and the median age was 59 years [IQR: 43-72]. The median age at the time of nephrotic syndrome diagnosis increased slightly through the decades (Table 1). The most common comorbidities in patients with nephrotic syndrome were prior thromboembolic disease (17%) and diabetes (15%), and from 1995-2000 to 2013-2018 the proportion of nephrotic syndrome patients with these and other comorbidities increased: diabetes (10% vs 20%), and thromboembolic disease (12% vs 20%) (Table 1).

Incidence

The overall incidence rate of nephrotic syndrome in adults was 3.85 per 100,000 person-years (95%-CI: 3.73-3.97) (Table 2). The incidence of nephrotic syndrome increased considerably with age (Figure 1), with the highest incidence rate being 11.77 per 100,000 person-years (95%-CI: 10.21-13.32) and 6.56 per

100,000 person-years (95%-CI: 5.71-7.41) observed in men and women 80+ years, respectively (eTable 1). The incidence of nephrotic syndrome was comparable in men and women below 50 years, but twofold higher in men than in women when above 50 years (Figure 1, eTable 1). During the study period the overall incidence increased from 3.35 per 100,000 person-years (95%-CI: 3.12-3.58) to 4.30 per 100,000 person-years (95%-CI: 4.05-4.54) (Table 2), with quite stable incidences in young adults (18-49 or 50-64 years), and somewhat increasing incidence in persons aged 65+ years (Figure 2).

Mortality

During the study period, 557 of the 3,970 patients with nephrotic syndrome died (Table 3), corresponding to an overall 1-year mortality of 14% (95%-CI: 13-15%), and 5-year mortality of 33% (95%-CI: 32-35%). The overall 1-year mortality of nephrotic syndrome remained stable over time (Table 3), but when accounting for changes in age and sex at diagnosis, the standardized 1-year mortality rate amongst those with nephrotic syndrome decreased from 19 per 100 person-years (95%-CI: 16-23) in 1995-2000 to 12 per 100 person-years (95%-CI: 10-14) in 2013-2018 (Figure 3). The decrease in mortality was greatest in the older age group (eFigure 2). Furthermore, the adjusted 1-year HR of death during 2013-2018 was 0.54 (95%-CI: 0.42-0.69) compared with 1995-2000 when adjusted for changes in case-mix of patients with nephrotic syndrome (Table 3). The mortality increased substantially with age from a 1-year mortality of 4% (95%-CI: 2-5%) in persons aged 40-49 years to 40% (95%-CI: 35-44 in persons 80+ years. The 1-year mortality increased with every type of comorbidity and with the highest risks of death associated with congestive heart failure (38% [95%-CI: 32-43]), chronic pulmonary disease (31% [95%-CI: 26-35]), and non-hematological cancer (32% [95%-CI: 26-37]) (eTable 2). The most common causes of death were cardiovascular disease (22%), cancer (18%), kidney or urological disease (14%), and endocrinological disease (13%) (eTable 3).

Pathology

In total, 52% of patients had a kidney biopsy in the context of nephrotic syndrome, and the proportion with biopsies increased during 1995-2018 (Table 1). Patients with a biopsy were younger and had less

comorbidity compared with those without a biopsy (eTable 4). Overall, the most common histopathological findings were membranous nephropathy (20%) and minimal change disease (20%) (Figure 4). Distribution of histopathological findings amongst patients with biopsies changed little over time, with slight increases of e.g. focal segmental glomerulosclerosis and diabetic nephropathy (Figure 4, eTable 5). Minimal change disease, and "other proliferative glomerulonephritis" were more common in young patients, whereas membranous nephropathy, focal segmental glomerulosclerosis, and "other glomerulonephritis" were more common in older patients (eFigure 3). In patients with kidney biopsies, the lowest 1-year mortality (between 5% and 6%) was observed with membranous nephropathy, other proliferative glomerulonephritis, focal segmental glomerulosclerosis, and minimal change disease, while the highest 1-year mortality was associated with non-glomerular conditions (14% [95%-CI: 6-22]) and other glomerulonephritis (20% [95%-CI: 15-25) (eTable 6).

Additional analyses

The increase in the incidence of recorded nephrotic syndrome from 1995 through 2018 observed in our main analysis followed periods of stable incidences from 1979 through 1994 in all age groups (eFigure 4). Of note, the decrease in the mortality in our main study period followed periods of consistently decreasing overall mortality from 1979 through 1994 (eFigure 5).

Discussion

Main Findings

This population-based cohort study shows that the incidence of recorded nephrotic syndrome is manifold higher in elderly than in young adults, and higher in men than in women. The overall incidence of nephrotic syndrome has increased since 1995, mainly driven by an increase among persons older than 65 years. The mortality of patients with nephrotic syndrome decreased markedly from 1995 to 2018, when accounting for changes in case-mix of patients, with a persistently low mortality in young adults, and a substantial reduction in the mortality among older people with nephrotic syndrome. Cardiovascular disease and cancer

were the most common underlying causes of death in nephrotic syndrome patients. The histopathological findings in biopsies in context of nephrotic syndrome did not change much during the study period, with each of membranous nephropathy and minimal change disease found in 1 in 5 patients.

Interpretation and previous studies

Although, we did not restrict our analyses to patients with kidney biopsies, we found only slightly higher incidence of nephrotic syndrome (3.85 per 100,000 person-years) than the previously reported annual incidences ranging from 0.58 to 4.2 per 100,000 adults in Europe and Australia.[12-21] The variation in nephrotic syndrome incidences may at least to some extent be explained by the variation in biopsy rates across countries, with e.g. 22-fold more biopsies in Finland than in Romania.[45] Importantly most estimates were based on historical data going up to six decades back.[12-16,18,19] Moreover, most prior studies were not restricted to first-time nephrotic syndrome patients,[12-14,17-19] and thus, may have included prevalent patients. Similar to our findings, an increase in nephrotic syndrome incidence with increasing age have previously been reported in France and Italy, but they were based on patients with biopsies and included few elderly patients.[14,16] A French study reported a small increase in nephrotic syndrome incidence over time from 3.6 per 100,000 person-years in 1976-1980, to 4.0 per 100,000 person-years in 1986-1990, but no updated figures have been reported.[15]

Previous studies of the mortality in patients with nephrotic syndrome are limited to patients with kidney biopsies.[21-29] These reported risks of death of 6-19% in patients with primary nephrotic syndrome during 5 years of follow-up,[22,23] and of 21% in patients with primary or secondary nephrotic syndrome during 3 years of follow-up.[21] Other studies examined mortality in patients with nephrotic syndrome and specific type of glomerulonephritis with reported 5-year mortality of 4-12% in those with minimal change disease,[22-24,26] 6-25% in those with membranous nephropathy,[22,23,25-27,29] and 3-22% in those with focal segmental glomerulosclerosis.[22,23,26] The large variation in the previously reported mortality of nephrotic syndrome patients may be explained by differences in study periods, loss to follow-up, exclusion criteria, or settings, and small sample sizes.[21-29] We found that nephrotic syndrome patients with kidney biopsy have lower

median age, and less comorbidity than those without biopsy, which may explain the generally lower mortality reported in previous studies. Furthermore, the mortality in patients with or without a biopsy are not directly comparable, as the acute mortality from time of presentation with nephrotic syndrome to a biopsy needs to be accounted for to avoid immortal time bias. We avoided such bias by starting follow-up at the latter of the dates of nephrotic syndrome and a biopsy.

The histopathological distribution among nephrotic syndrome patients in our study is in line with previous reporting from Japan and England,[46,47] with minimal change disease being more common in young adults and membranous nephropathy being more common in elderly. During the past decades increased prevalence of focal segmental glomerulosclerosis among nephrotic syndrome patients has been reported in the USA,[48,49] but we observed only small increases in the predominantly white Danish population. The small increase in biopsy verified diabetic nephropathy over time despite a considerable increase in the proportion of diabetes among patients with nephrotic syndrome, may be explained by the lower biopsy rate among individuals with comorbidity.[50] The reasons for- and the consequences of the lower biopsy rate in subsets of nephrotic syndrome patients (e.g. very elderly, or patients with diabetes) needs to be addressed in future studies.[45]

The markedly decreased mortality of nephrotic syndrome from 1995 to 2018 may be explained by changes in patient composition (e.g. if more benign nephrotic syndrome events are recorded in recent years), improved treatment of nephrotic syndrome (i.e. introduction of biological treatment or improvement of steroid regiments), or improved prevention and treatment of thromboembolic and other complications of nephrotic syndrome. A previous study showed that mortality of myocardial infarction in Denmark in 2008 was less than half of that in 1984.[51] In line with findings from Scotland,[21] we found cardiovascular disease to be the most common cause of death among patients with nephrotic syndrome. Hence, improved treatment and prophylaxis of thromboembolic complications of nephrotic syndrome likely explains some of the decrease in the mortality of nephrotic syndrome during the study period.

Limitations

Nationwide high quality registry data allowed us to examine the age- and sex-specific epidemiology of incident nephrotic syndrome through 24 years with a minimal loss to follow-up. Yet, some limitations need consideration. We included patients with recorded nephrotic syndrome, so we did not capture patients with nephrotic syndrome without a formal diagnosis, and as the sensitivity and specificity of the nephrotic syndrome ICD-10 code is unknown, we may have under- or overestimated of the incidence and mortality. Hence, we cannot rule out that greater awareness of nephrotic syndrome, and increased diagnostic activity in the more recent years contributed to the observed increased incidence and decreased mortality of nephrotic syndrome over time. As comorbidity information in the early study period was based on inpatient data only before 1995, an increase in data availability in combination with better diagnostic tools, and more complete recording may contribute to the observed increasing prevalence of comorbidities in patients with nephrotic syndrome. Our findings from the additional analyses, including data preceding the study period, indicates that the main findings of an increasing incidence and decreasing mortality was not due to intermittent fluctuations. Yet, better diagnostic tools and more complete recording may in part explain the increase in incidence and decrease in mortality of nephrotic syndrome from 1979 through 1994.

We lacked data on lifestyle factors (e.g. smoking, BMI, alcohol, and diet) and clinical details (e.g. blood pressure measurements, and glomerular filtration rate). Such factors may contribute to the changes in incidence and mortality of nephrotic syndrome over time. The time dependent increase in the incidence of nephrotic syndrome is similar to the reported increase in the prevalence of overweight among Danes with a similar, higher prevalence in men than in women.[52] Furthermore, improved management of hypertension, cancer and diabetes as well as decreases in tobacco and alcohol consumption in Danish adults may explain some of the decrease in mortality over time. The influence of lifestyle on incidence and mortality of nephrotic syndrome should be explored in future studies.

Future studies not only based on kidney biopsy registries are needed, to examine if our findings are generalizable to populations with different healthcare systems and demographic compositions.

Conclusion

Using population-based nationwide data, we showed that the incidence of recorded nephrotic syndrome increases strongly with age, and the incidence increased from 1995 through 2018. When accounting for changes in case-mix of patients, the 1- and 5-year mortality of nephrotic syndrome nearly halved during this period, despite a high mortality in older patients, and patients with comorbidity. The distribution of glomerulopathies was stable over time but differed across age groups. More awareness and more complete recording of nephrotic syndrome may have contributed to these observed changes in incidence and mortality over time. With the expected further ageing of the population and increased prevalence of risk factors for nephrotic syndrome we predict that the incidence of nephrotic syndrome will increase in future.

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Disclosures

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Data availability statement

According to Danish legislation, we are not allowed to distribute or make the patient data used in the current study directly available to other parties.

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Tables

Table 1. Characteristics of 3,970 adults with first-time nephrotic syndrome in Denmark during 1995-2018.

	Calendar periods of diagnosis				
	1995-2000	**2001-2006**	**2007-2012**	**2013-2018**	**Total**
	n=837	n=987	n=982	n=1,164	n=3,970
Male sex, n (%)	462 (55)	576 (58)	556 (57)	658 (57)	2,252 (57)
Age, median [IQR]	56 [40, 70]	58 [42, 70]	59 [41, 72]	63 [48, 75]	59 [43, 72]
Age group					
18-29 years	107 (13)	92 (9)	92 (9)	109 (9)	400 (10)
30-39 years	106 (13)	123 (12)	131 (13)	99 (9)	459 (12)
40-49 years	106 (13)	145 (15)	151 (15)	120 (10)	522 (13)
50-59 years	156 (19)	190 (19)	138 (14)	197 (17)	681 (17)
60-69 years	153 (18)	181 (18)	199 (20)	227 (20)	760 (19)
70-79 years	136 (16)	162 (16)	159 (16)	241 (21)	698 (18)
80+ years	73 (9)	94 (10)	112 (11)	171 (15)	450 (11)
Place of diagnosis					
Emergency Room	17 (2)	19 (2)	15 (2)	21 (2)	72 (2)
Inpatient	588 (70)	709 (72)	721 (73)	695 (60)	2,713 (68)
Outpatient	232 (28)	259 (26)	246 (25)	448 (38)	1,185 (30)
Kidney diagnoses during 10 years prior to nephrotic syndrome index date					
Glomerulonephritis (excl. nephrotic syndrome), n (%)	108 (13)	100 (10)	99 (10)	102 (9)	409 (10)
Renal tubulointerstitial diseases, n (%)	40 (5)	48 (5)	36 (4)	46 (4)	170 (4)
Acute kidney injury or chronic kidney disease, n (%)	59 (7)	119 (12)	142 (14)	174 (15)	494 (12)
Hypertensive nephropathy, n (%)	24 (3)	25 (3)	14 (1)	14 (1)	77 (2)
Diabetic nephropathy, n (%)	22 (3)	50 (5)	45 (5)	75 (6)	192 (5)
Comorbidity diagnoses during 10 years prior to nephrotic syndrome index date					
Diabetes, n (%)	86 (10)	140 (14)	147 (15)	238 (20)	611 (15)
Chronic liver disease, n (%)	14 (2)	21 (2)	16 (2)	34 (3)	85 (2)
Chronic pulmonary disease, n (%)	57 (7)	80 (8)	89 (9)	116 (10)	342 (9)
Connective tissue disease, n (%)	61 (7)	63 (6)	62 (6)	68 (6)	254 (6)
Congestive heart failure, n (%)	71 (8)	79 (8)	68 (7)	91 (8)	309 (8)
Thromboembolic disease, n (%)	100 (12)	169 (17)	180 (18)	230 (20)	679 (17)
Non-hematological cancer, n (%)	47 (6)	77 (8)	63 (6)	108 (9)	295 (7)
Hematological cancer, n (%)	25 (3)	25 (3)	33 (3)	64 (5)	147 (4)
Pregnancy at index date [a], n (%)	30 (8)	27 (7)	31 (7)	29 (6)	117 (7)
Kidney biopsy +/- 180 days from diagnosis, n (%)	388 (46)	483 (49)	552 (56)	637 (55)	2,060 (52)

IQR, interquartile range

[a]Percentages of women

Table 2. Crude and standardized incidence of recorded nephrotic syndrome in Denmark during 1995-2018, overall and by time period (standardized to the age and sex profile of the Danish population in year 2000).

	First-time events, n	Person-time at risk, person-years	Incidence rate per 100,000 person-years (95% CI)	Standardized incidence rate per 100,000 person-years (95% CI)
Overall	3,970	103,089,000	3.85 (3.73-3.97)	3.74 (3.62-3.86)
By period				
1995-2000	837	24,970,925	3.35 (3.12-3.58)	3.37 (3.14-3.60)
2001-2006	987	25,195,310	3.92 (3.67-4.16)	3.86 (3.62-4.10)
2007-2012	982	25,834,778	3.80 (3.56-4.04)	3.68 (3.45-3.92)
2013-2018	1,164	27,087,987	4.30 (4.05-4.54)	4.04 (3.81-4.28)

Table 3. One and five year absolute mortality and hazard ratio of death in 3,970 patients with first-time recorded nephrotic syndrome overall and by calendar period and age group

	1-year					5-year			
	No. of patients, n	No. of deaths, n	Mortality, % (95% CI)	HR unadjusted (95% CI)	HR adjusted [a] (95% CI)	No. of deaths, n	Mortality, % (95% CI)	HR unadjusted (95% CI)	HR adjusted [a] (95% CI)
Overall	3,970	557	14% (13-15)	-	-	1,264	33% (32-35)	-	-
Calendar period									
1995-2000	837	121	14% (12-17)	ref.	ref.	286	34% (31-37)	ref.	ref.
2001-2006	987	158	16% (14-18)	1.11 (0.88-1.41)	0.98 (0.78-1.25)	344	35% (32-38)	1.03 (0.88-1.20)	0.90 (0.77-1.06)
2007-2012	982	131	13% (11-15)	0.91 (0.71-1.17)	0.73 (0.57-0.94)	301	31% (28-34)	0.87 (0.74-1.03)	0.69 (0.58-0.81)
2013-2018	1,164	147	13% (11-15)	0.85 (0.67-1.09)	0.54 (0.42-0.69)	333	35% (32-38)	0.95 (0.81-1.11)	0.57 (0.48-0.67)
Age group									
18-29 years	400	<10 [b]	-	0.12 (0.04-0.32)	0.14 (0.05-0.38)	18	5% (3-7)	0.18 (0.11-0.29)	0.22 (0.13-0.35)
30-39 years	459	<10 [b]	-	0.20 (0.10-0.43)	0.23 (0.11-0.48)	26	6% (4-8)	0.22 (0.15-0.34)	0.26 (0.17-0.39)
40-49 years	522	19	4% (2-5)	0.43 (0.26-0.73)	0.46 (0.27-0.77)	56	11% (8-14)	0.43 (0.32-0.59)	0.46 (0.34-0.63)
50-59 years	681	56	8% (6-10)	ref.	ref.	156	24% (21-27)	ref.	ref.
60-69 years	760	112	15% (12-17)	1.86 (1.35-2.56)	1.77 (1.28-2.44)	277	39% (35-42)	1.76 (1.45-2.14)	1.73 (1.42-2.11)
70-79 years	698	179	26% (22-29)	3.42 (2.53-4.61)	2.98 (2.20-4.04)	378	57% (53-61)	3.17 (2.63-3.82)	2.90 (2.40-3.51)
80+ years	450	179	40% (35-44)	5.93 (4.40-8.01)	5.06 (3.70-6.90)	353	82% (77-85)	5.84 (4.83-7.06)	5.43 (4.46-6.61)

[a]Adjusted for age (in calendar period strata only), sex, calendar year (in age group strata only), and prior diabetes, liver disease, pulmonary disease, connective tissue disease, congestive heart failure, thromboembolic disease, non-hematological cancer, and hematological cancer

[b]Due to Danish legislation, the exact number in cells containing small numbers cannot be reported.

Figures

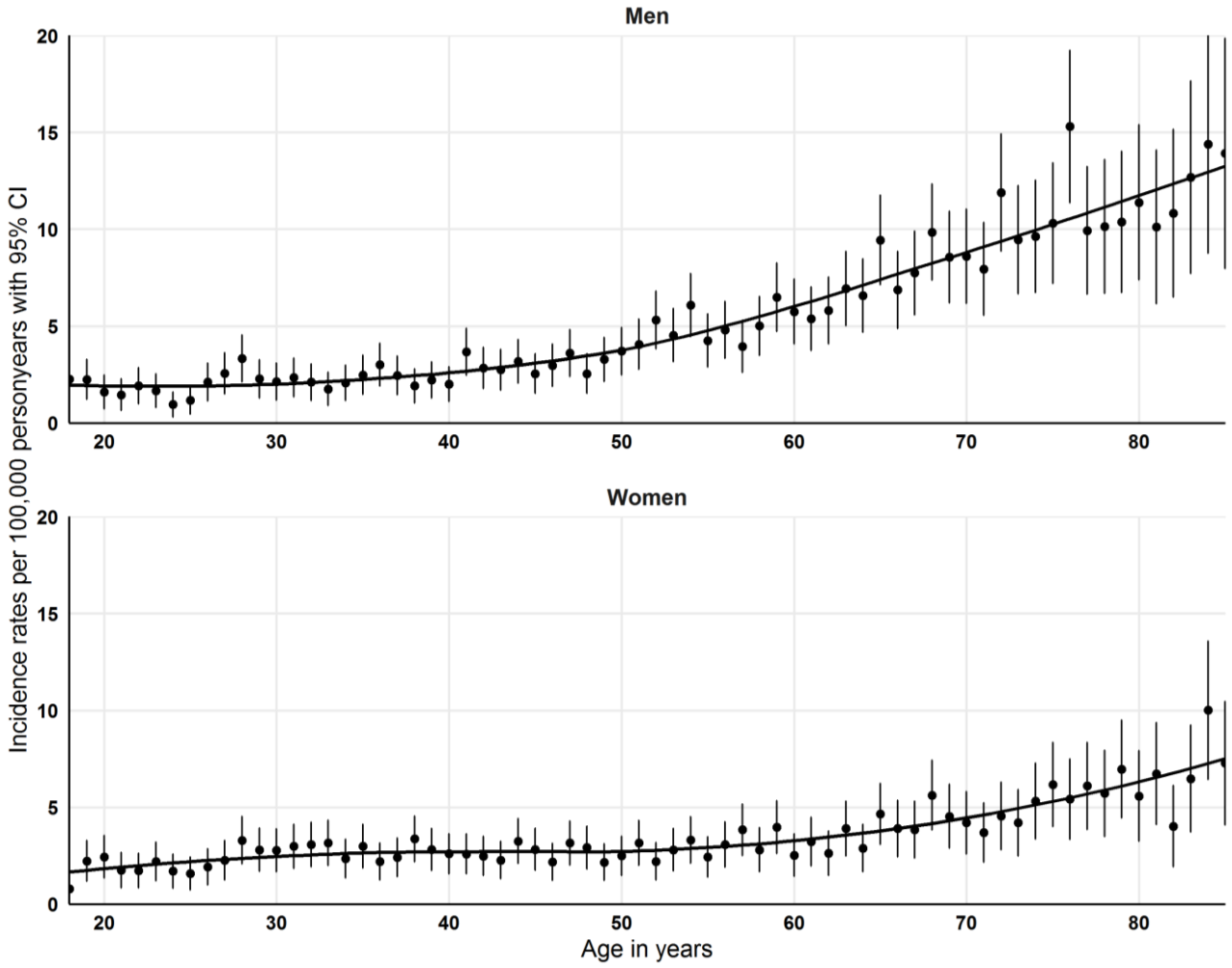

Figure 1. Incidence rates of recorded nephrotic syndrome men and women over ages from 18 to 85 years in Denmark during 1995-2018.

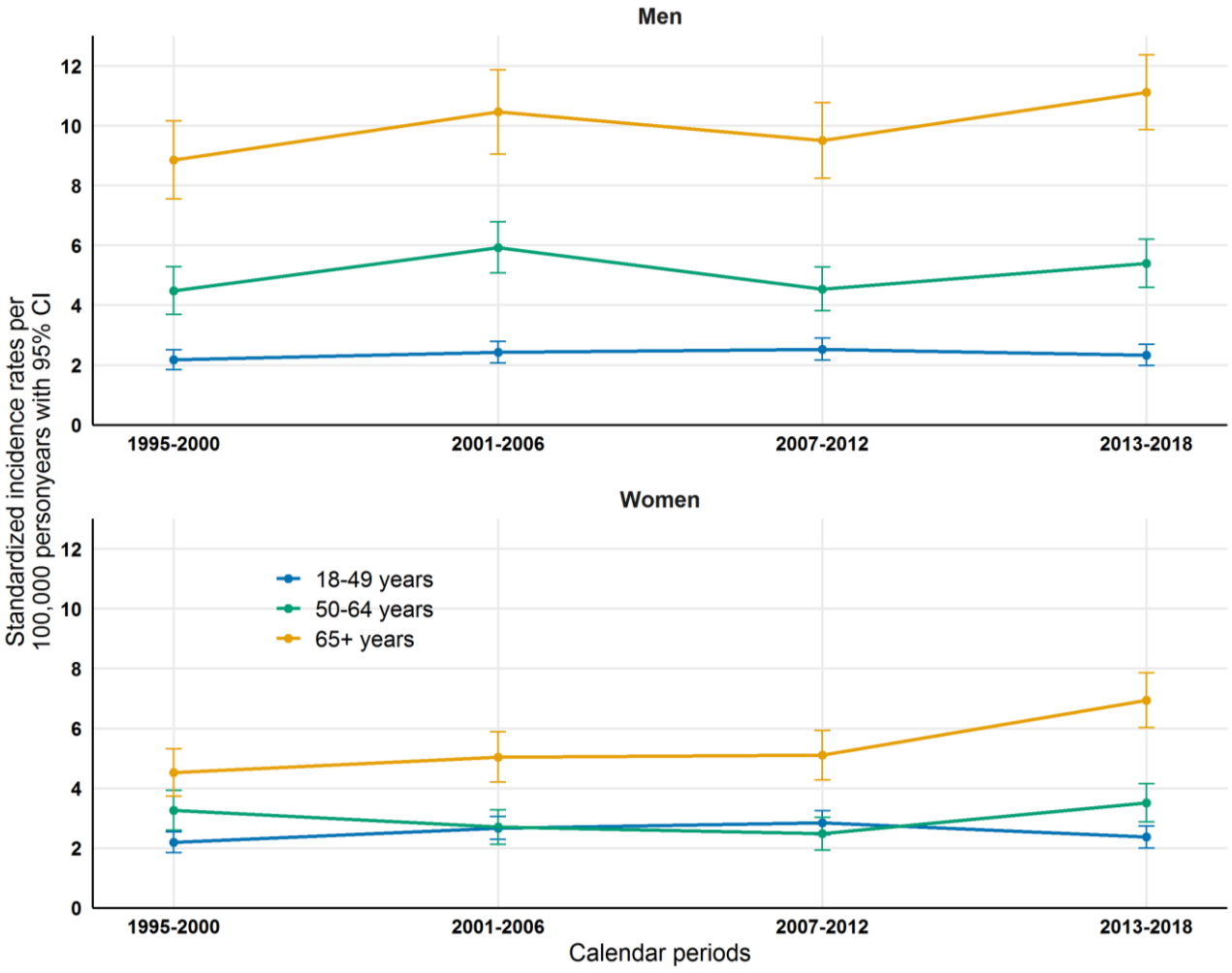

Figure 2. Standardized incidence rates of recorded nephrotic syndrome in adult men and women by calendar period from 1995 through 2018 stratified by age group.

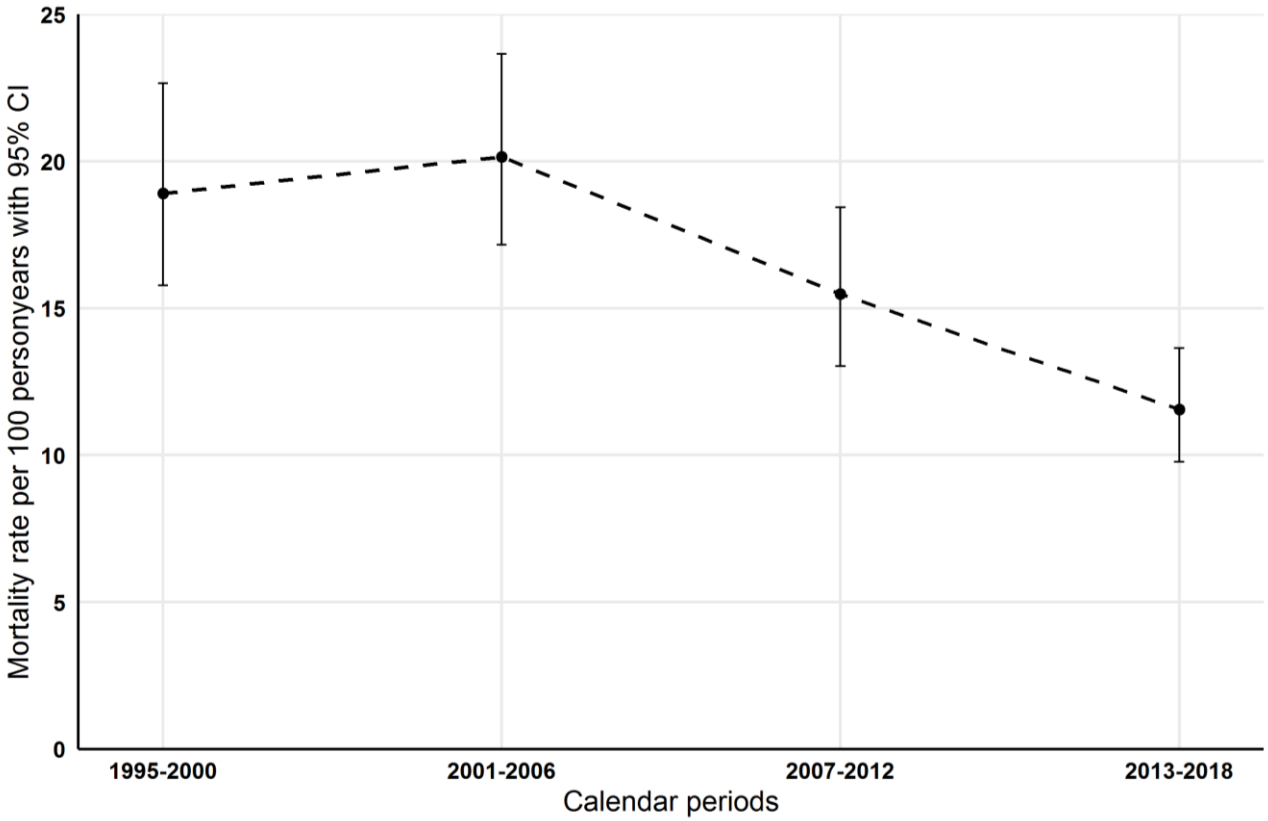

Figure 3. Standardized 1-year mortality rate per 100 person-years among 3,970 patients with first-time recorded nephrotic syndrome in Denmark from 1995 through 2018. Direct standardization with internal weights by sex and 10-year age group.

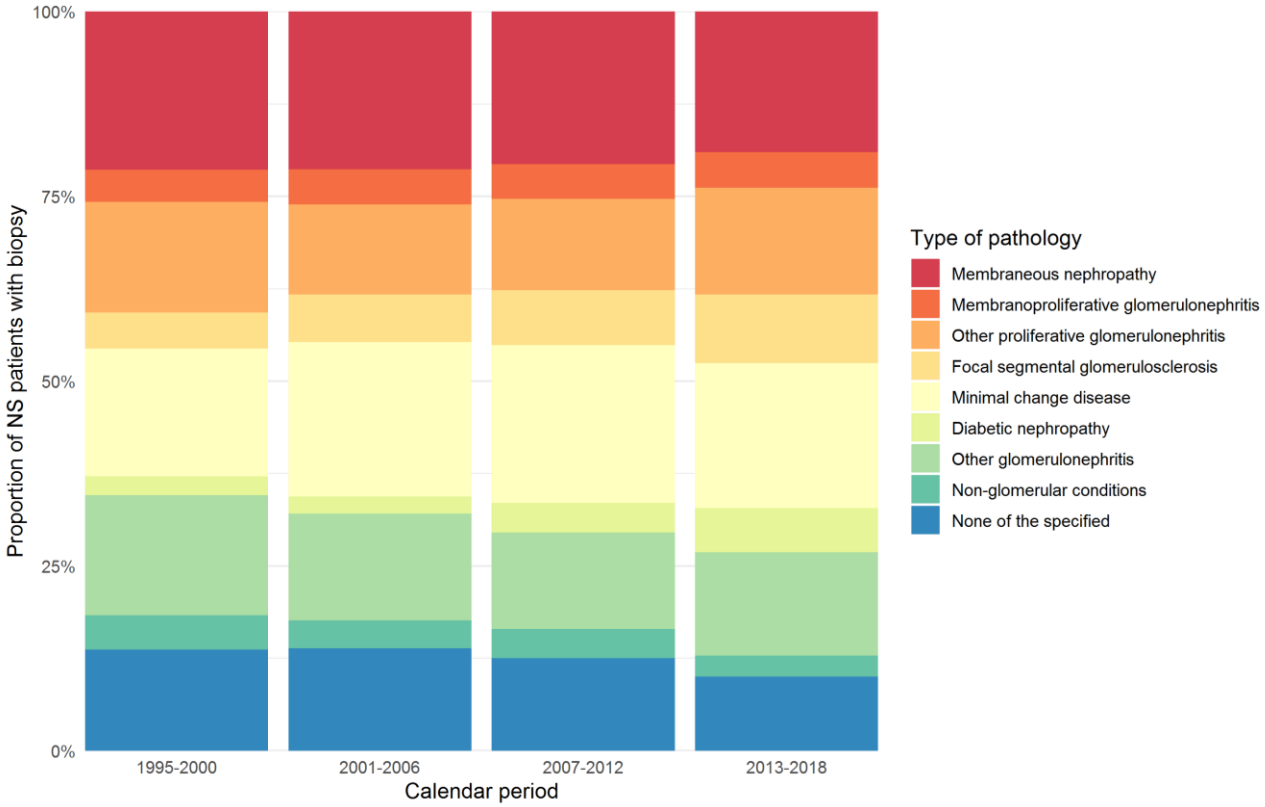

Figure 4. Proportion of patients with each type of histopathological findings by calendar period in 2,060 adults with kidney biopsies within +/-180 days from first-time recorded nephrotic syndrome. In patients with more than one biopsy, the type of pathology refers to the findings recorded in the biopsy closest to index date.