

eAPPENDICES

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CODEBOOKS

Nephrotic syndrome

Patients with recorded nephrotic syndrome were identified using the following codes specific to nephrotic syndrome.

Condition	ICD-8	ICD-10
Nephrotic Syndrome	581	N04

Prior Kidney Diagnoses

Codes for identifying comorbidities recorded up to 10 years before nephrotic syndrome index date.

Condition	ICD-8	ICD-10
Glomerulonephritis (excl. nephrotic syndrome)	580; 582-583	N00-N03; N05-N08
Renal tubulointerstitial diseases	590; 593.19	N10-N16
Acute kidney injury and chronic kidney disease	792; 584	N17-N19
Hypertensive nephropathy	403-404	I12; I13
Diabetic nephropathy	249.02; 250.02	E102; E112; E122; E132; E142

Prior Diagnosed Comorbidities

Codes for identifying comorbidities recorded up to 10 years before nephrotic syndrome index date.

Condition	ICD-8	ICD-10
Any diabetes	249; 250	E10-E14
Liver disease	571; 573.01; 573.04; 070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B18; B19.0; K70-K74; K76.0; K76.6; I85
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Any connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Thromboembolic disease	410-412; 433-434; 436.01; 436.90; 440-445; 450-453	I21-I23; I26; I63-I64; I70-I74; I77; I80-I82; K550H
Non-hematological cancers (excl. non-melanoma skin cancer)	140-172, 174-199	C00-C43, C45-C75
Hematological cancers	200-207; 275.59	C81-C96; D473, D752, D459, D471, D474; D46;

Kidney Transplantation

Codes for identifying and excluding patients with kidney transplantation before nephrotic syndrome index date.

Condition	Procedure codes	NOMESCO	ICD-10
Kidney transplant	57480; 57490;	KKAS	Z940; T861

Pregnancy

We excluded women with ongoing pregnancy at nephrotic syndrome index date, by excluding patients with codes suggesting “pregnancy” recorded from 280 days before to 280 days after index date, or “abortion” from index date to 140 days after index date, or “child delivery” recorded from index date to 280 days after index date.

Covariate	Description	Time window	ICD-8	ICD-10
Ongoing pregnancy	Pregnancy	From 280 days before to 280 after index	630-639	O09-O49; Z32-Z36
	Abortion	From index to 140 days after index	640-645	O00-O08
	Child delivery	From index to 280 days after index	650-662	O60-O84; Z37-Z39

Histopathology

Each person was included in no more than one histopathological group based on the findings in kidney biopsies performed within 180 days from the nephrotic syndrome index date. If several biopsies were performed in the same patient, the biopsy closest to the nephrotic syndrome index date was selected. In case of multiple histopathological findings in the same biopsy, the histopathological classification was based on the finding listed first in the table below. The descriptive code had to be recorded with the procedure code for kidney tissue (T71).

<https://www.patobank.dk/kodebog/?tag=M>

Group	GNs included in group	Pathological description	Code descriptive	Code tissue
Membranous nephropathy (MN)	Membranous nephropathy	Membranous glomerulonephritis	M68130	T71
Membranoproliferative glomerulonephritis	Membranoproliferative glomerulonephritis	Membranoproliferative glomerulonephritis	M46842	T71
		Dense deposit disease	M46844	T71
Other proliferative glomerulonephritis	Mesangioproliferative glomerulopathy	Mesangioproliferative glomerulonephritis	M46862	T71
		IgA-glomerulonephritis	S67300	T71
	Proliferative endocapillary glomerulonephritis	Endocapillary proliferative glomerulonephritis	M46870	T71
		Post infectious glomerulonephritis	S67410	T71
Unspecified proliferative glomerulonephritis	Proliferative glomerulonephritis	M46810	T71	
Focal segmental glomerulosclerosis (FSGS)	Focal segmental glomerulosclerosis	Focal segmental glomerulosclerosis	M53341	T71
		Focal segmental glomerulosclerosis, cellular type	M53342	T71
		Focal segmental glomerulosclerosis, collapsing type	M53343	T71
		Focal segmental glomerulosclerosis, tip lesion	M53344	T71
Minimal change disease (MCD)	Minimal change disease	Normal tissue	M00100	T71
		Minimal change disease	S67550	T71
		Foot process fusion	M53440	T71
Diabetic nephropathy	Diabetic nephropathy	Diabetic nephropathy	S67700	T71
		Nodular intercapillary glomerulosclerosis	M53320	T71
Other glomerulonephritis	Deposition glomerulonephritis	Amyloid deposit	M55100	T71
		Light chain cast disease	M55120	T71
		Light chain deposit disease	M55130	T71
		Fibrillary glomerulonephritis	M55170	T71
		Immunotactoid glomerulopathy	M55180	T71
		Fibronectin glomerulopathy	M55190	T71
		AA amyloidosis	S38930	T71
		AL amyloidosis	S38940	T71
	Necrotizing and crescentic glomerulonephritis and vasculitis (extracapillary glomerulonephritis)	Extracapillary glomerulonephritis	M46880	T71
		Wegener's granulomatosis	S76950	T71
		ANCA-associated glomerulonephritis	S67420	T71
		Anti-GBM glomerulonephritis	S67400	T71
	Other/unspecified glomerulonephritis	Focal glomerulonephritis	M46861	T71
		Glomerulonephritis NOS	M46801	T71
		Glomerular half-moon	M4680A	T71
		Glomerulosclerosis	M53300	T71
		Diffuse intercapillary glomerulosclerosis	M53312	T71
Focal segmental proliferative glomerulonephritis		M46811	T71	
Non-glomerular conditions	Non-glomerular conditions (Interstitial and/or tubular inflammation/necrosis, fibrosis)	Acute and chronic inflammation	M42100	T71
		Chronic inflammation	M43000	T71
		Follicular inflammation	M43080	T71
		Non-necrotizing granulomatous inflammation	M44200	T71
		Granulation tissue	M45020	T71
		Ischemia-reperfusion injury	M52700	T71
		Acute ischemic nephropathy	M53150	T71
		Acute tubular damage	M53160	T71
		Ischemic acute tubular necrosis	S67630	T71
		IgG4-related disease	S47414	T71
	Fibrosis	M49000	T71	
	Hypertensive nephropathy and thrombotic microangiopathies	Arteriolosclerosis with fibrinoid necrosis	M52210	T71
		Hyaline arteriolosclerosis	M52250	T71
		Thrombotic microangiopathy	M53420	T71
		Hemolytic, uremic syndrome	S42940	T71

SUPPLEMENTARY TABLES

eTable 1. Incidence rates of recorded nephrotic syndrome from 1995 through 2018 in Denmark stratified by sex and age-group.

Sex	Age-group	First-time events, n	Persontime at risk, PYs	Incidence rate per 100,000 PYs, IR (95% CI)
Men	18-29 years	198	10,089,604	1.96 (1.69- 2.24)
	30-39 years	207	9,226,051	2.24 (1.94- 2.55)
	40-49 years	278	9,476,281	2.93 (2.59- 3.28)
	50-59 years	421	8,780,479	4.79 (4.34- 5.25)
	60-69 years	493	6,870,205	7.18 (6.54- 7.81)
	70-79 years	434	4,248,583	10.22 (9.25-11.18)
	80+ years	221	1,878,261	11.77 (10.21-13.32)
	Women	18-29 years	202	9,768,156
30-39 years		252	8,977,010	2.81 (2.46-3.15)
40-49 years		244	9,248,287	2.64 (2.31-2.97)
50-59 years		260	8,698,690	2.99 (2.63-3.35)
60-69 years		267	7,177,842	3.72 (3.27-4.17)
70-79 years		264	5,159,290	5.12 (4.50-5.73)
80+ years		229	3,490,261	6.56 (5.71-7.41)

PY, personyears; IR, incidence rate

eTable 2. One-year mortality in 3,970 patients with recorded nephrotic syndrome during 1995-2018, stratified by comorbidity diagnosed up to 10 years before nephrotic syndrome index date

	No. at risk	No. of deaths	1 year mortality risk, % (95% CI)	Unadjusted hazard ratio of death (95% CI)	Adjusted hazard ratio of death* (95% CI)
Diabetes					
No	3359	446	13% (12-14)	ref.	ref.
Yes	611	111	18% (15-21)	1.40 (1.14-1.73)	1.27 (1.02-1.57)
Chronic liver disease					
No	3885	541	14% (13-15)	ref.	ref.
Yes	85	16	19% (10-27)	1.39 (0.84-2.28)	1.79 (1.08-2.95)
Chronic pulmonary disease					
No	3628	452	12% (11-14)	ref.	ref.
Yes	342	105	31% (26-35)	2.74 (2.22-3.39)	1.56 (1.25-1.94)
Connective tissue disease					
No	3716	508	14% (13-15)	ref.	ref.
Yes	254	49	19% (14-24)	1.45 (1.08-1.94)	1.33 (0.99-1.79)
Congestive heart failure					
No	3661	441	12% (11-13)	ref.	ref.
Yes	309	116	38% (32-43)	3.74 (3.05-4.59)	1.54 (1.24-1.92)
Thromboembolic disease					
No	3291	375	11% (10-12)	ref.	ref.
Yes	679	182	27% (23-30)	2.63 (2.20-3.13)	1.40 (1.16-1.69)
Non-hematological cancer					
No	3675	464	13% (12-14)	ref.	ref.
Yes	295	93	32% (26-37)	2.79 (2.23-3.48)	1.85 (1.48-2.32)
Hematological cancer					
No	3823	518	14% (12-15)	ref.	ref.
Yes	147	39	27% (19-33)	2.12 (1.53-2.94)	1.62 (1.17-2.24)

*Adjusted for sex, age, calendar year, and prior diabetes, liver disease, pulmonary disease, connective tissue disease, congestive heart failure, thromboembolic disease, non-hematological cancer, and hematological cancer

eTable 3. Recorded cause of death in the 1,869 deceased patients of the 3,970 patients with recorded nephrotic syndrome during 1995-2018.

ICD-10 chapter	Chapter description	number of deaths, n	proportion of total deaths, %
A	Certain infectious and parasitic diseases	35	2 %
B	Certain infectious and parasitic diseases	17	1 %
C	Malign neoplasms	330	18 %
D	Benign neoplasms and diseases of the blood and blood forming organs	26	1 %
E	Endocrine, nutritional and metabolic diseases	246	13 %
F	Mental, Behavioral and Neurodevelopmental disorders	47	3 %
G	Diseases of the nervous system	18	1 %
I	Diseases of the circulatory system	420	22 %
J	Diseases of the respiratory system	133	7 %
K	Diseases of the digestive system	67	4 %
L	Diseases of the skin and subcutaneous tissue	n<10	-
M	Diseases of the musculoskeletal system and connective tissue	28	1 %
N	Diseases of the genitourinary system	270	14 %
O	Pregnancy, childbirth and the puerperium	n<10	-
Q	Congenital malformations, deformations and chromosomal abnormalities	10	1 %
Others*	-	104	6 %
Missing cause of death	-	113	6 %

*Including chapters R, S, T, X, Y, and Z with "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified", "Injury, poisoning and certain other consequences of external causes", "Codes for special purposes", "External causes of morbidity", "Factors influencing health status and contact with health services".

eTable 4. Characteristics of 1,910 patients without and 2,060 patients with a kidney biopsy in context of first-time nephrotic syndrome in Denmark during 1995-2018.

	Biopsy +/- 180 days from nephrotic syndrome index date	
	No	Yes
	n=1,910	n=2,060
Male sex, n (%)	1,021 (53)	1,231 (60)
Age, median [IQR]	63 [45, 77]	56 [41, 68]
Age-group		
18-29 years	165 (9)	235 (11)
30-39 years	216 (11)	243 (12)
40-49 years	216 (11)	306 (15)
50-59 years	276 (14)	405 (20)
60-69 years	300 (16)	460 (22)
70-79 years	363 (19)	335 (16)
80+ years	374 (20)	76 (4)
Calendar period of diagnosis		
1995-2000	449 (24)	388 (19)
2001-2006	504 (26)	438 (23)
2007-2012	430 (23)	552 (27)
2013-2018	527(28)	637 (31)
Place of diagnosis		
Emergency Room	56 (3)	16 (1)
Inpatient	1,150 (60)	1,563 (76)
Outpatient	704 (37)	481 (23)
Kidney diagnoses during 10 years prior to nephrotic syndrome index date		
Glomerulonephritis (excl. nephrotic syndrome), n (%)	214 (11)	195 (9)
Renal tubulointerstitial diseases, n (%)	133 (7)	37 (2)
Acute kidney injury or chronic kidney disease, n (%)	341 (18)	153 (7)
Hypertensive nephropathy, n (%)	55 (3)	22 (1)
Diabetic nephropathy, n (%)	137 (7)	55 (3)
Comorbidity diagnoses during 10 years prior to nephrotic syndrome index date		
Diabetes, n (%)	378 (20)	233 (11)
Chronic liver disease, n (%)	48 (3)	37 (2)
Chronic pulmonary disease, n (%)	191 (10)	151 (7)
Connective tissue disease, n (%)	123 (6)	131 (6)
Congestive heart failure, n (%)	212 (11)	97 (5)
Thromboembolic disease, n (%)	427 (22)	252 (12)
Non-hematological cancer, n (%)	165 (9)	130 (6)
Hematological cancer, n (%)	74 (4)	73 (4)
Pregnancy at index date*	74 (8)	43 (5)

*Percentages of women

eTable 5. Histopathological findings in 2,060 patients with kidney biopsies within 180 days before or after the date of first-time recorded nephrotic syndrome. All percentages are column-percentages, counting only patients with kidney biopsies in the denominator.

	Calendar periods of nephrotic syndrome diagnosis			
	1995-2000	2001-2006	2007-2012	2013-2018
Any kidney biopsy	388 (100)	483 (100)	552 (100)	637 (100)
Type of glomerulopathy				
Membranous nephropathy	83 (21)	103 (21)	114 (21)	121 (19)
Membranoproliferative glomerulonephritis	17 (4)	23 (5)	26 (5)	31 (5)
Other proliferative glomerulonephritis	58 (15)	59 (12)	68 (12)	92 (14)
Focal segmental glomerulosclerosis	19 (5)	31 (6)	41 (7)	59 (9)
Minimal change disease	67 (17)	101 (21)	118 (21)	125 (20)
Diabetic nephropathy	10 (3)	11 (2)	22 (4)	38 (6)
Other glomerulonephritis*	63 (16)	70 (14)	72 (13)	89 (14)
Non-glomerular conditions	18 (5)	18 (4)	22 (4)	18 (3)

* Including: Deposition glomerulonephritis, Necrotizing and crescentic glomerulonephritis and vasculitis (extracapillary glomerulonephritis), and Other/unspecified glomerulonephritis

eTable 6. One- and five-year mortality in 2,047 patients* with biopsy in context of first-time recorded nephrotic syndrome by type of glomerulopathy. Follow-up started at nephrotic syndrome index date or date of biopsy whichever came latest to avoid immortal time (as biopsies were assessed +/- 180 days from nephrotic syndrome index date).

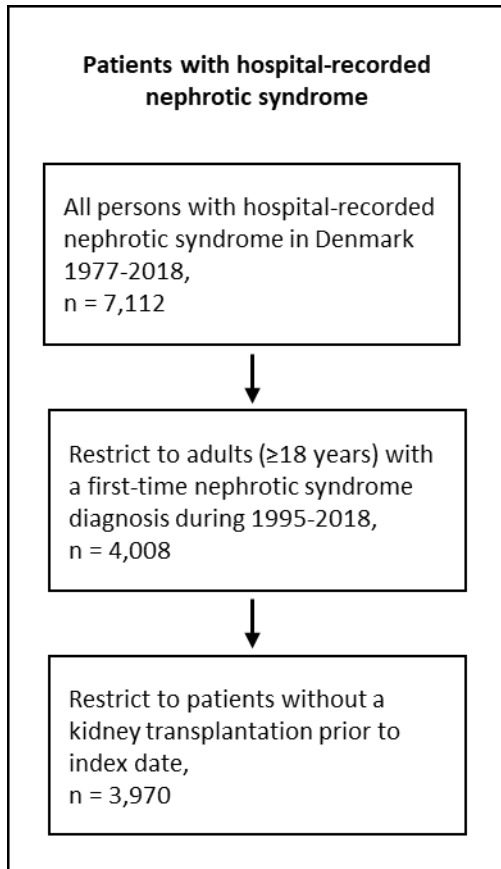
Type of glomerulopathy	1-year					5-year			
	No. at risk at time of biopsy, n	No. of deaths, n	Mortality risk, % (95% CI)	HR unadjusted (95% CI)	HR adjusted** (95% CI)	No. of deaths, n	Mortality risk, % (95% CI)	HR unadjusted (95% CI)	HR adjusted** (95% CI)
Membranous nephropathy	419	24	6% (3-8)	ref.	ref.	60	15% (12-19)	ref.	ref.
Membranoproliferative glomerulonephritis	97	9	9% (3-15)	1.66 (0.77-3.58)	2.16 (1.00-4.65)	19	21% (12-29)	1.42 (0.85-2.39)	1.81 (1.08-3.04)
Other proliferative glomerulonephritis	277	12	4% (2-7)	0.75 (0.38-1.50)	1.05 (0.52-2.10)	44	17% (12-22)	1.10 (0.74-1.62)	1.53 (1.04-2.26)
Focal segmental glomerulosclerosis	150	9	6% (2-10)	1.04 (0.48-2.23)	1.05 (0.49-2.27)	31	22% (15-29)	1.50 (0.97-2.32)	1.69 (1.09-2.60)
Minimal change disease	411	20	5% (3-7)	0.85 (0.47-1.53)	1.07 (0.59-1.95)	49	13% (9-16)	0.81 (0.56-1.18)	1.04 (0.71-1.51)
Diabetic nephropathy	80	9	11% (4-18)	1.99 (0.93-4.29)	3.16 (1.46-6.86)	28	39% (27-50)	2.98 (1.90-4.67)	4.57 (2.91-7.19)
Other glomerulonephritis***	288	58	20% (15-25)	3.78 (2.35-6.09)	3.14 (1.95-5.06)	127	47% (40-52)	3.80 (2.80-5.17)	3.45 (2.54-4.69)
Non-glomerular conditions	76	11	14% (6-22)	2.56 (1.26-5.23)	1.74 (0.85-3.56)	24	33% (21-43)	2.37 (1.47-3.80)	1.74 (1.08-2.80)
None of the specified	249	22	9% (5-12)	1.57 (0.88-2.79)	1.40 (0.78-2.49)	58	25% (19-30)	1.69 (1.18-2.43)	1.65 (1.15-2.37)

* Out of the 2,060 patients with a biopsy around nephrotic syndrome index date, 13 patients were excluded as they died before the recorded date of the biopsy, i.e. before start of follow-up.

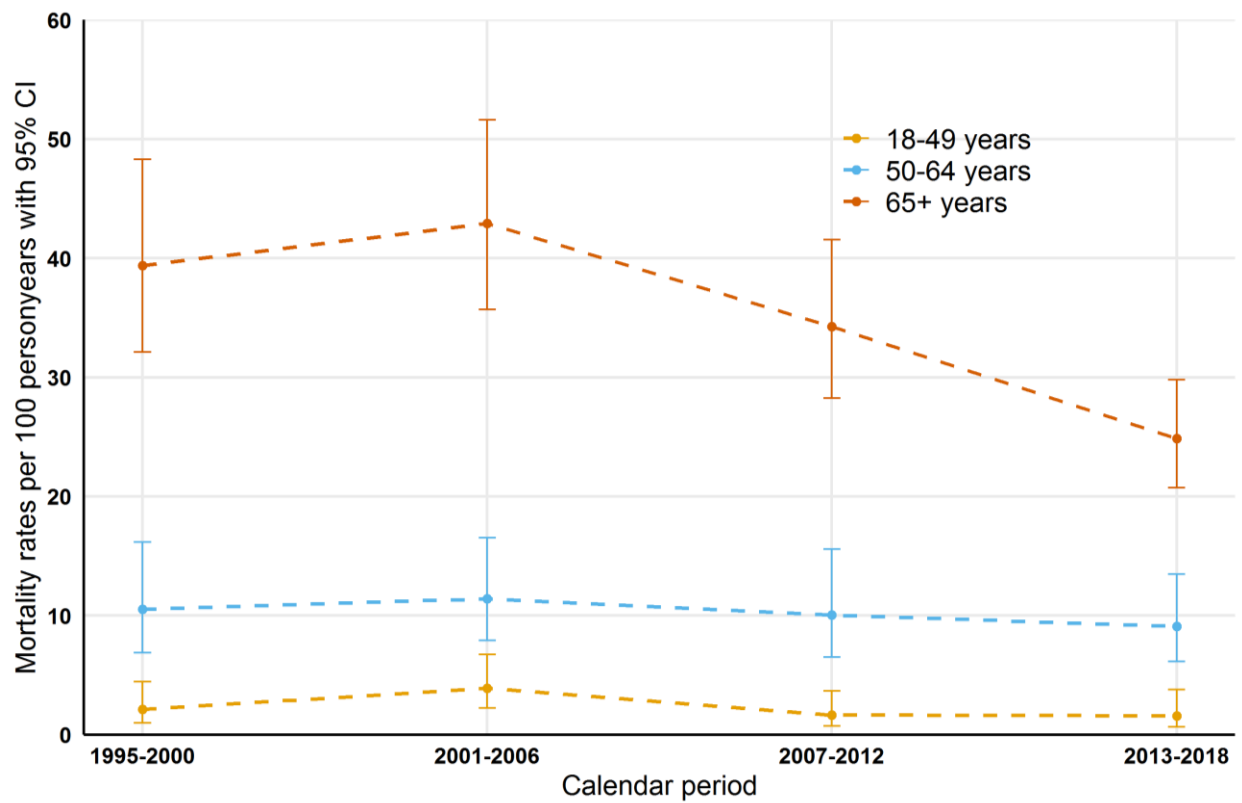
** Adjusted for age and calendar-year

*** Including: Deposition glomerulonephritis, Necrotizing and crescentic glomerulonephritis and vasculitis (extracapillary glomerulonephritis), Other/unspecified glomerulonephritis

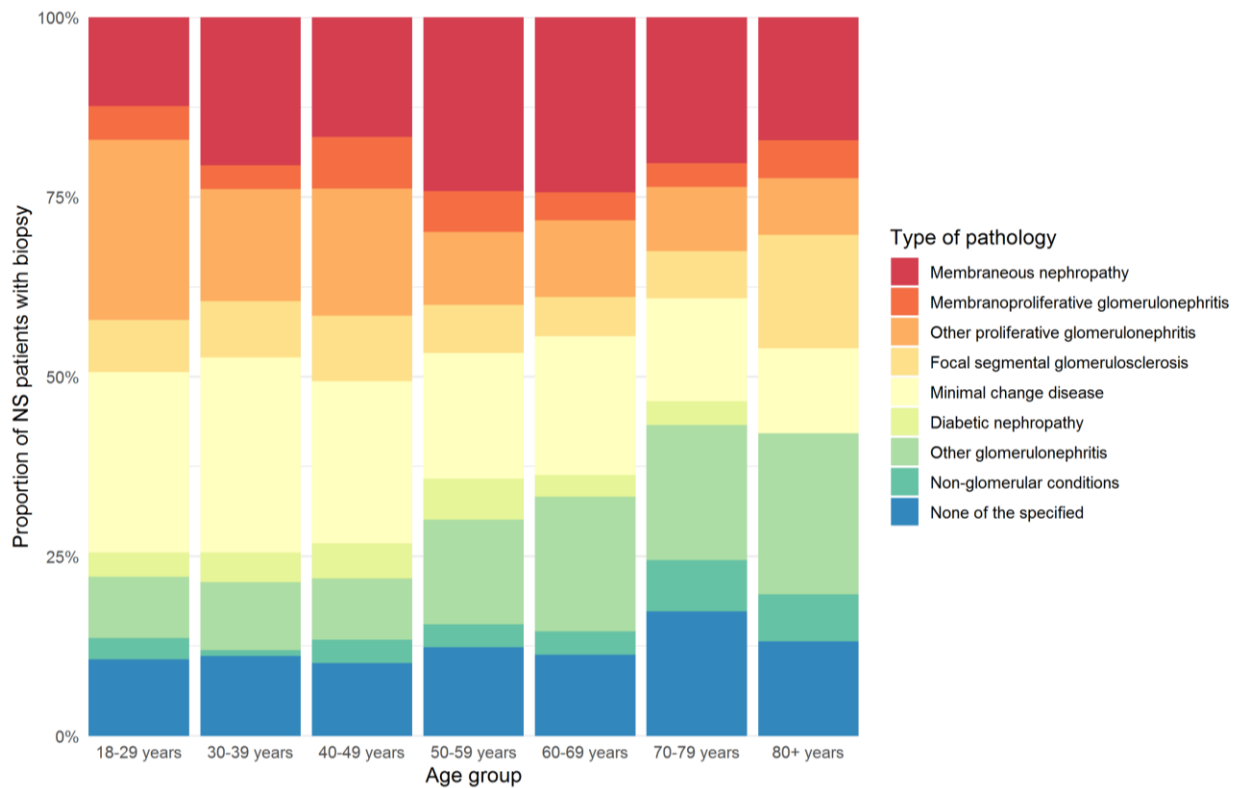
SUPPLEMENTARY FIGURES



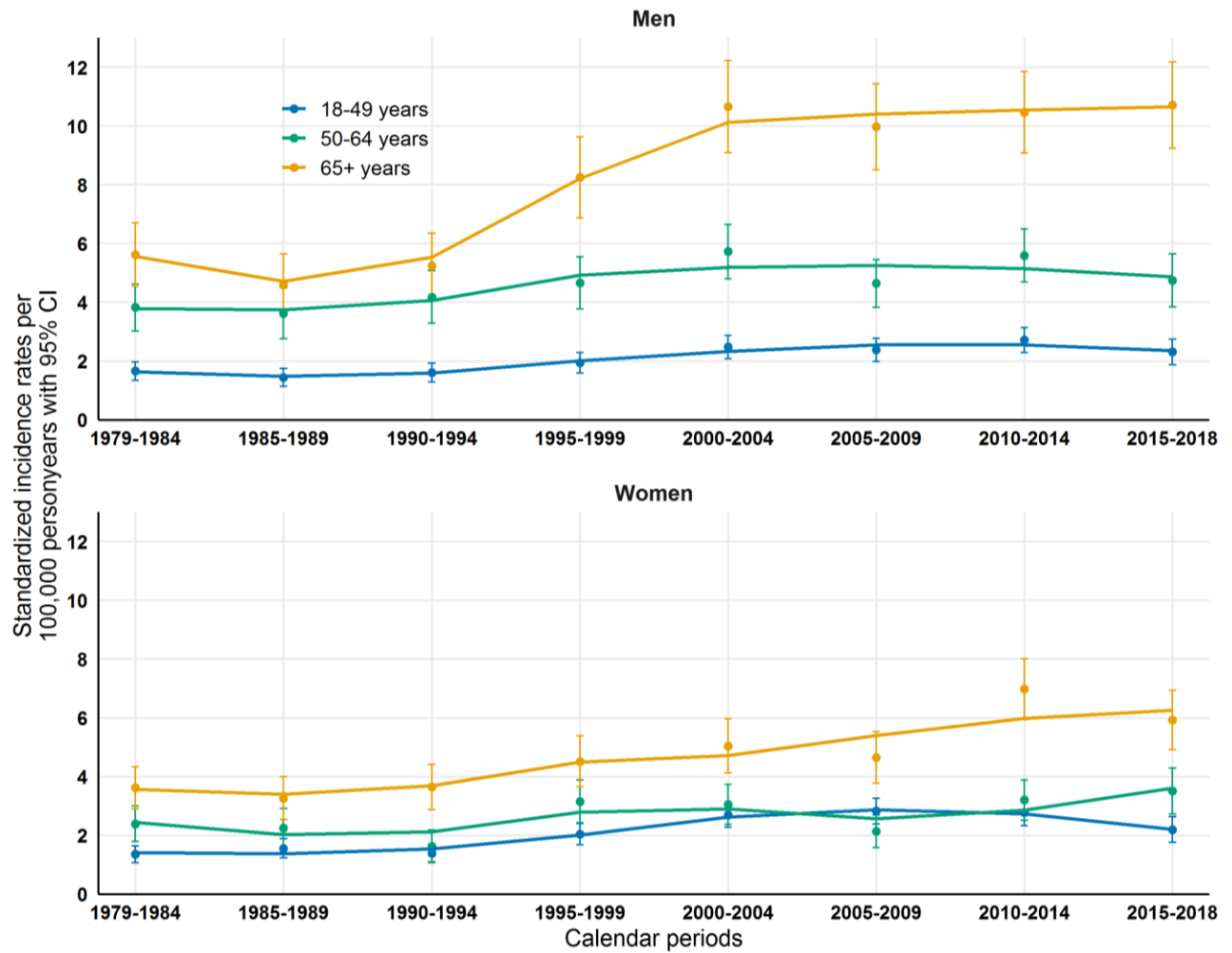
eFigure 1. Flowchart of inclusion



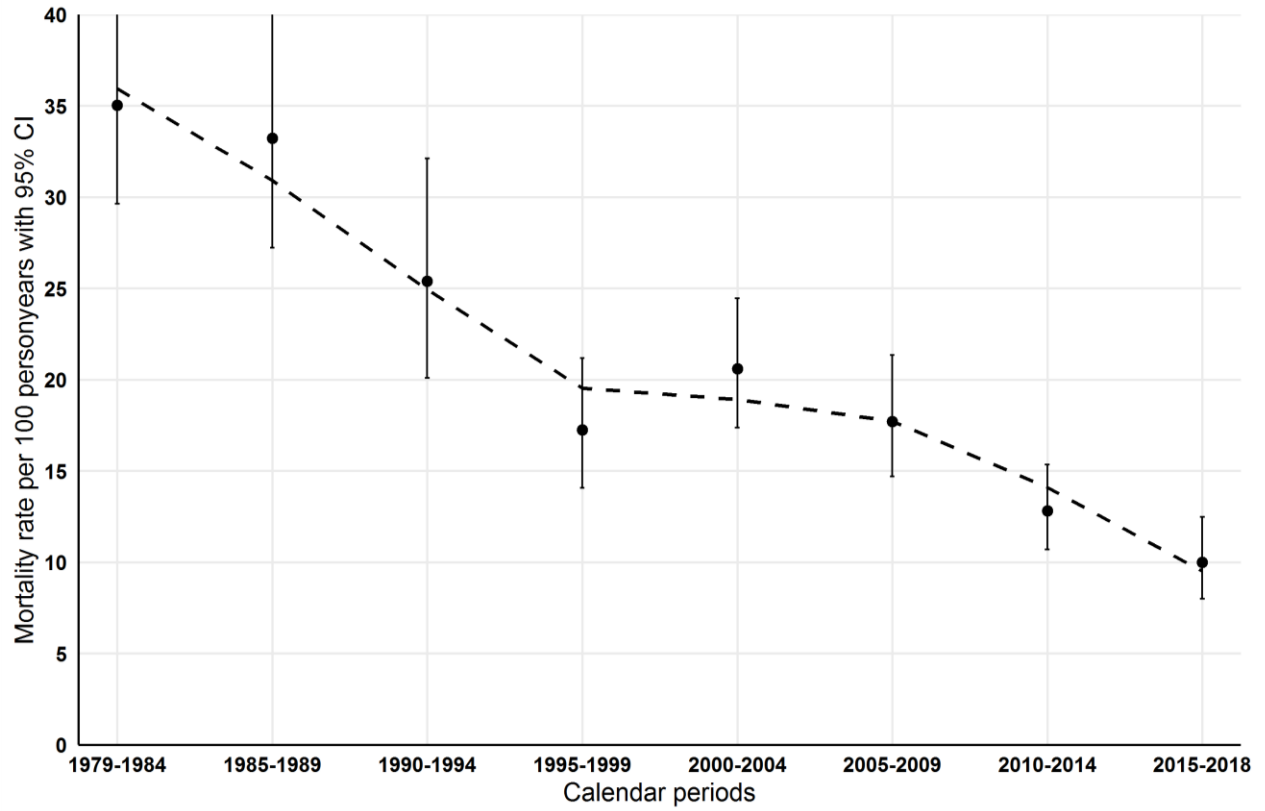
eFigure 2. Standardized mortality rates in adult men and women with recorded nephrotic syndrome from 1995 through 2018 standardized by sex and stratified by age-group.



eFigure 3. Proportion of patients with each type of histopathological findings by age-groups in 2,060 patients with kidney biopsies taken +/-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.



eFigure 4. Standardized incidence rates of recorded nephrotic syndrome in adult men and women by calendar period from 1979 through 2018 stratified by age group (fitted curve smoothed with loess function).



eFigure 5. Standardized 1-year mortality rate per 100 person-years among 5,446 patients with first-time recorded nephrotic syndrome in Denmark from 1979 through 2018 (fitted curve smoothed with loess function). Direct standardization with internal weights by sex and 10-year age group.