Hematuria and subsequent long-term risk of end-stage kidney disease:

A Danish population-based cohort study

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Abstract

Background: Hematuria is a frequent incidental clinical finding and may be a symptom of pre-existing underlying benign or malignant urinary tract or kidney disease. However, in patients with no apparent underlying cause of hematuria, long-term prognosis of hematuria remains unknown.

Objectives: To assess the long-term risk of end-stage-kidney disease (ESKD) in patients with a hospital-based hematuria diagnosis and no apparent underlying cause.

Methods: Patients with a hospital diagnosis of hematuria were included and matched in a 1:5 ratio with comparison persons from the background population by age, sex and residency. We calculated the cumulative risk of ESKD considering death as a competing risk. Furthermore, we computed unadjusted and adjusted hazard ratios with 95% confidence intervals using Cox hazard regression with adjustment for age, sex, and comorbidities.

Results: We included 170,189 hematuria-diagnosed patients. The absolute 10-year risk of ESKD was 0.7% (95%CI: 0.7-0.8) in patients with hematuria and 0.4% (95%CI: 0.3-0.4) in comparison persons, hence yielding an overall adjusted hazard ratio of 1.6 (95%CI: 1.4-1.7). Hematuria also increased the risk of EKSD in patients with pre-existing comorbidities like diabetes (adjusted HR: 1.3 [95%CI: 1.1-1.5]) and urogenital cancer (adjusted HR: 1.4 ([95%CI: 1.1-1.9]), whereas no association was observed in patients with previous kidney disease (adjusted HR: 0.9 (95%CI: 0.8-1.0).

Conclusion: A hospital-based hematuria diagnosis in patients with no apparent underlying cause of hematuria is a marker of an increased risk of future ESKD.

Key words: Kidney Failure, Chronic; Hematuria; Epidemiology; Cohort studies; Risk factor

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Introduction

Hematuria is a frequent incidental clinical finding; Its prevalence ranges between 0.2% and 32% across subgroups of the population[1, 2]. Presence of hematuria may be associated with an occult underlying benign or malignant condition stemming from any site along the urinary tract, however in two out of three referred patients, the aetiology of hematuria remains unclear after diagnostic work-up[3].

Unlike proteinuria, which is a widely-accepted marker for kidney damage, the natural history of hematuria is not explained solely by glomerular dysfunction, since blood in urine may arise from either glomerular disease or from pathology further along the urinary tract[4]. Controversy thus exists around appropriate evaluation, management and prognosis of hematuria and strong evidence is lacking as to whether hematuria might be a marker of future kidney disease.

Yet, hematuria has been associated with increased risk of kidney disease in individuals where initial work-up revealed no apparent underlying cause of an abnormal dipstick finding[4-7].

A large nationwide population-based study examined the long-term risk of end-stage kidney disease (ESKD – earlier denoted ESRD) among Israeli adolescents and persistent asymptomatic isolated microscopic hematuria was associated with an 18-fold increased ESKD risk[5]. Similar results, though less evident, have been reported by three smaller cohort studies conducted on East Asian populations evaluating long-term risk of chronic kidney disease (CKD), ESKD or kidney function deterioration among patients with microscopic hematuria[6-8]. All previous studies however, investigated selected subpopulations using volunteer recruitment and most of them were limited by small sample sizes and loss to follow-up. Combined with different aetiologies of CKD and ESKD in a European setting, the previously reported data may be difficult to extrapolate to Western populations[9, 10].

In a hospital setting, the long-term prognosis of patients with no apparent underlying cause of a hematuria diagnosis remains unclarified. This nationwide cohort study aimed to examine if a hospital-based hematuria diagnosis is a potential marker of increased risk of ESKD risk among patients with no apparent cause of hematuria.

Material and Methods

Setting and data sources

We conducted a nationwide population-based cohort study within Denmark (with a population of approximately 5.8 million) from 1 January 1998 through 31 December 2018. We used prospectively collected routine data from population-based registries. Information from the Danish National Patient Registry (DNPR) was linked at individual level using unambiguous identification numbers from the Civil Registration System (CRS) with encoded information on sex and date of birth[11]. In Denmark, the Danish National Health Service provides tax-supported healthcare for the entire population, guaranteeing free and uniform access to general practitioners and hospital care[12].

The DNPR holds records of all non-psychiatric hospitalizations since 1977 and emergency room contacts and outpatient visits since 1995. Each contact comprises data on date of admission and discharge, surgical procedures performed, and discharge diagnoses coded according to the Eighth Edition of the *International Classification of Disease* (ICD-8) through 1993 and the Tenth Revision (ICD-10) thereafter[13]. One primary diagnosis (ie. the main reason for hospitalization) is recorded and optionally secondary diagnoses from diseases related to the current hospital visit (e.g. underlying chronic diseases or additional findings from the current work-up).

This study was registered at Aarhus University (record number 2016-051-000001/812). According to Danish legislation, registry-based studies do not require approval from an Ethics Committee or informed consent from patients.

Study participants

From the DNPR, we identified all patients assigned a first-time diagnosis of hematuria (both primary and secondary diagnoses) from 1 January 1998 through 31 December 2017. All hospital-based diagnoses of hematuria recorded during hospitalizations, outpatient visits, or contacts to emergency rooms were included and date of discharge was defined as index date (ICD-10: R31, ICD-8: 789.39; Table S1). We did not include patients with a hematuria diagnosis describing pathologically verified kidney abnormalities (ICD-10: N02 *Recurrent and persistent hematuria,* Supplemental Figure S1).

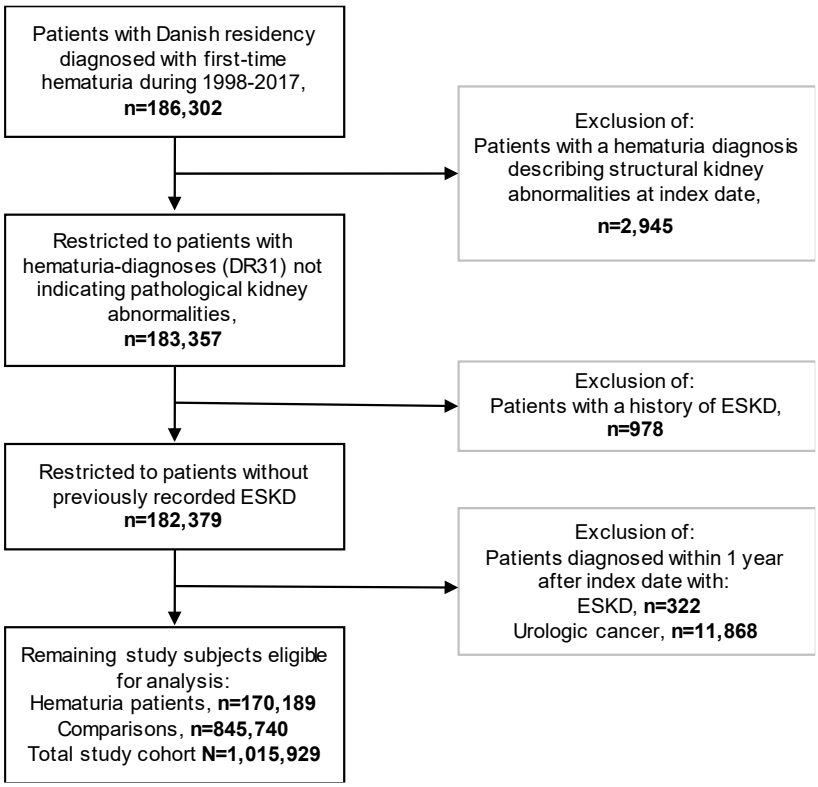


Figure S1 *Flow chart of eligible patients included in the analysis*

For each patient with hematuria, we randomly selected five comparison persons from the general Danish population matched on age, sex and region of residency at index date (Supplemental Figure S2). Comparison persons were assigned the same index date as their corresponding patient with hematuria and had to be alive and with no previously registered hematuria diagnosis at index date (Supplemental Figure S2).

We excluded hematuria patients and comparison persons with ESKD before index date and those who received a diagnosis of ESKD or urological cancer within the first year after index date. This was done to avoid including patients with prevalent ESKD or urological cancer, which was detected during the diagnostic process following the hematuria diagnosis (Supplemental Table S1 for ICD-codes, Supplemental Figure S2).

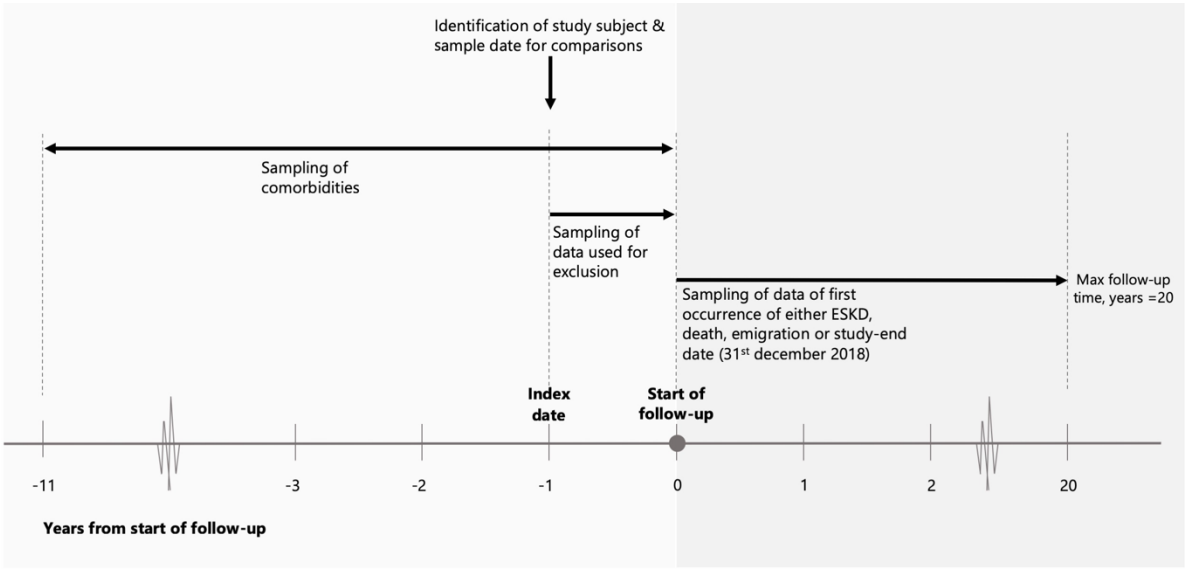


Figure S2 *Study design*

Outcome

Through DNPR, we identified occurrence of ESKD defined as the first admission date with a code for any form of renal replacement therapy (RRT) (Table S1 for codes). Initiation of renal replacement therapy i.e. hemodialysis, peritoneal dialysis or kidney transplantation, hence treated ESKD, is a valid proxy for kidney failure used in other studies (estimated glomerular filtration rate of <15 ml/min/1.73 m^2)[14]. Follow-up was censored at death, emigration or the end of study period through linkage to CRS.

Covariates

We obtained information on the following characteristics at index date: Age groups (<20, 20-39, 40-59, 60-79, and ≥80), sex, type of hospital care (inpatient, outpatient and emergency room visits), and year (index date during 1998-2002, 2003-2007, 2008-2012, or 2013-2017). For each patient, previous comorbidity was sampled from the DNPR during 10 years prior to and up to 1 year following the index date (Supplemental Figure S2). Comorbidities were aggregated into the following categories with potential impact on ESKD risk: (i) kidney disease, except cancer; (ii) urogenital disease, except cancer; (iii) urogenital or kidney cancer; (iv) other cancer; (v) diabetes mellitus; (vi) hypertension; (vii) cardiovascular disease; and (viii) connective tissue disease (Supplemental Table S1 for codes). Furthermore, we used DNPR to identify in- and outpatient contacts for chronic obstructive pulmonary disease (COPD), as an indicator of smoking status (Table S1).

Discharge diagnoses	ICD-8 codes (1977-1993)	ICD-10 codes (since 1994)
Identification of study subjects		
Hematuria		
Unspecified	789.39	DR31
Macroscopic		DR31.9A
Microscopic		DR31.9B
Characterization of study subjects		
Kidney disease (excl. cancer)	24902 25002 580 581 582 583 584 59009 59320 59324 75310 75311 75319	DN00 DN01 DN02 DN04 DN05 DN06 DN14 DN15 DN16 DN17 DN18 DN19 DN25 DN26 DN27 DN280 DN281 DN288A DN288C DN288H DN288J DN290 DN298 DI120 DI129 DI131 DI132 DI139 DI150 DI151 DR392 DQ611 DQ612 DQ613 DQ614 DN083 DE102 DE112 DN07 DN08 DN03 DN11
Urogenital diseases (excl. cancer)	592 594 59319 600 601 602	DN13 DN20 DN21 DN22 DN23 DN288B DN288G DN301 DN302 DN304 DN31 DN32 DN33 DN34 DN35 DN36 DN37 DN38 DN391 DN392 DN393 DN394 DN395 DN396 DN397 DN398 DN399 DN40 DN41 DN42 DN7 DN8
Urogenital & kidney cancers (excluding CIS[a] except for bladder)	184.09 180 182 183 185 189.29 189.19 189.09 188	DC52-DC56 DC57.0-DC57.4 DC61 DC64-DC66 DC679 DC68 DD090 DD303
Other cancer (solid tumor, leukemia, lymphoma and metastatic tumor)	14-18 191-194 204-207 200-203 275.59 195-199	DC1-DC7 DC81 DC82 DC83 DC84 DC85 DC88 DC9 Excluding codes from the above urogenital and kidney cancers
Chronic obstructive lung disease (COPD)	490-492	DJ43-DJ44
Diabetes Mellitus	249.00 249.06 249.07 249.09 250.00 250.06 250.07 250.09	DE100 DE101 DE103 DE104 DE105 DE106 DE107 DE108 DE109 DE110 DE111 DE113 DE114 DE115 DE116 DE117 DE118 DE119 DE12 DE13 DE14 DO240 DO241 DO242 DO243 DO245 DO249 DG632 DH360
Hypertension	400 401 402	DI10 I152 I158 I159
Cardiovascular disease	344 411 413 410 427.09 427.10 427.11 427.19 428.99 78249 430 431 433 434 435 440 441 442 443 444 445 45100 394 395 396 397 398 427.93 427.94	DI11 DI20 DI130 DI251 DI259 DI21 DI50 DI63 DI60 DI61 DI62 DG459 DI64 DI70 DI71 DI72 DI73 DI74 DI77 DI801 DI802 DI803 DI26 DI05 DI06 DI07 DI080 DI098 DI34 DI35 DI36 DI37 DI390 DI393 DI511A DQ22 DI48 G81 G82
Connective tissue disease	712 716 734 446 135.99	DM05 DM06 DM08 DM09 DM30 DM31 DM32 DM33 DM34 DM35 DM36 DD86
Urinary tract infection		N300 DN303 DN308 DN309 DN33 DN34 DN39 DN390 DN10 DN12 DN136 DN288D DN288E DN288F DN291
Urogenital or kidney procedures/ surgeries		KK KTK KUK
Identification of Outcomes		
End-stage kidney disease		
Chronic dialysis		BJFD2
Kidney transplantation		KKAS
Identification of covariates used for sensitivity analyses		
Kidney disease	580 581 584 59009 59320 59324 75310 75311 75319	DN00 DN01 DN02 DN04 DN05 DN06 DN14 DN15 DN16 DN17 DN25 DN26 DN27 DN280 DN281 DN288A DN288C DN288H DN288J DN290 DN298 DI129 DI139 DI150 DI151 DQ611 DQ612 DQ613 DQ614 DN083 DE102 DE112 DN07 DN08 DN03 DN11 DN18 DN19 DR392 DI120 DI131 DI132
Urogenital and kidney cancer	184.09 180 182 183 185 189.29 189.19 189.09 188	DC52-DC56 DC57.0-DC57.4 DC61 DC64-DC66 DC679 DD090 DD303
Kidney biopsy		KKAB KUKA05

Table S1: *Discharge diagnoses codes used to identify study subjects, characterize comorbidity and identify outcome*

Lastly, we also obtained data from the DNPR on recent urinary tract infection (within 1 month before the index date) and urogenital or kidney instrumentation (within 3 months before the index date) to clarify possible apparent causes of hematuria (Supplemental Table S1).

Statistical Analyses

We tabulated patient characteristics including demography, year of hematuria diagnosis/index date, type of hospital care, type of hematuria, the medical specialty issuing the hematuria diagnosis, and previous comorbidities for the hematuria patients and comparison persons, respectively.

Follow-up started 1 year after the index date and continued until first occurrence of ESKD, death, emigration, or 31 December 2018, whichever occurred first.

We calculated the 5- and 10-year absolute risk of ESKD as cumulative incidence proportion (CIP) treating death as a competing risk[15]. CIPs were stratified by sex, age group, type of hospital care, comorbidities and type of hematuria.

To compare the risk of ESKD between hematuria patients and comparison persons, a Cox regression model was used to estimate both unadjusted and adjusted hazards ratios and associated 95% confidence intervals (CIs). The assumption of the proportional hazard was examined using log-log plots and was found to be valid.

For both unadjusted and adjusted analyses, we stratified the overall result by age, sex, type of hematuria and comorbidities. Of note, in some strata, the unadjusted analyses were adjusted for the matching variables by design due to the matching process.

We adjusted for all covariates except for the matching factors that remained intact within the stratum concerned.

To consider biopsy-triggered hematuria, we excluded patients with a kidney biopsy performed any time before index date as a sensitivity analysis. Furthermore, we calculated the overall adjusted HR after exclusion of patients with a history of kidney disease, or cancer of the kidneys or the urogenital tract up to 10 years before and 1 year after index date.

All statistical analyses were conducted using the statistical software package Stata version 15.1 (Stata Corp, College Station, Texas, USA).

Results

Descriptive data

We included 170,189 patients with a first-time hospital hematuria diagnosis from 1998 through 2017, after exclusion of 2,945 patients with diagnosis codes indicating pathologically verified kidney abnormality, 978 patients with a history of ESKD and lastly 322 and 11,868 patients, receiving an ESKD diagnosis or urologic cancer diagnosis within 1 year from index date, respectively. These 170,189 patients were matched to 845,740 comparison persons from the general population (Supplemental Figure S1).

The prevalence of baseline characteristics and comorbidities are tabulated in Table 1. Overall, the median age at index date was 61 years (IQR: 46-73) and 60.4% were men. Patients with hematuria were more likely to have a history of urogenital disease (33.4% vs. 10.2%), urogenital or kidney cancer (8.2% vs. 2.3%), hypertension (17.3% vs. 11.4%), and cardiovascular disease (27.8% vs. 18.8%). Among hematuria patients, 5% had a diagnosis of urinary tract infection within 1 month before and 7.6% had a urogenital or kidney procedure performed within 3 months before hematuria diagnosis. In addition, 0.06% (n=105) of the hematuria patients had a kidney biopsy performed any time before the hematuria.

Absolute risk of end-stage kidney disease

We observed an ESKD diagnosis in 978 (0.6%) of the hematuria patients and in 2,395 (0.3%) of the comparison persons during the median follow-up of 6.3 years (IQR: 3.0-11.1).

During follow-up, the overall risk of ESKD among hematuria patients increased from 0.4% (95%CI: 0.4-0.5) after 5 years to 0.7% (95%CI: 0.7-0.8) after 10-years (Table 2, Figure 1). Same tendencies were observed for comparison persons as well as across stratifications. The overall 10-year risk of ESKD was higher in hematuria patients (CIP: 0.7% [95% CI: 0.7-0.8]) than in comparisons (CIP: 0.4% [95% CI: 0.3-1.4]) (Table 2, Figure 1).

The absolute risk of ESKD were generally low in both cohorts, however male sex, previous kidney disease and pre-existing diabetes mellitus or hypertension were associated with higher absolute risk of ESKD irrespective of exposure group (Table 2). The absolute risk of ESKD in both cohorts increased with higher age and was subsequently observed to decrease in the oldest age group (>79 years) (Table 2). When stratified by comorbidity the

Characteristics	Hematuria cohort, n (%)	Comparison cohort, n (%)
N	170,189	845,740
Sex, n (%)		
Male	102,839 (60.43)	509,944 (60.30)
Female	67,350 (39.57)	335,796 (39.70)
Age at index date, n (%)		
<20	8,661 (5.09)	43,270 (5.12)
20-39	21,169 (12.44)	105,901 (12.52)
40-59	49,483 (29.08)	246,896 (29.19)
60-79	66,994 (39.36)	331,883 (39.24)
>79	23,882 (14.03)	117,790 (13.93)
Year at index date, n (%)		
1998-2002	33,127 (19.46)	164,873 (19.49)
2003-2007	37,140 (21.82)	184,518 (21.82)
2008-2012	47,552 (27.94)	236,176 (27.93)
2013-2017	52,370 (30.77)	260,173 (30.76)
Baseline comorbidities registered up to 11 years prior to and 1 year after start of follow-up, n (%)		
Kidney disease (except cancer)	9,557 (5.62)	14,980 (1.77)
Urogenital disease (except cancer)	56,812 (33.38)	86,307 (10.20)
Urogenital or kidney cancer	13,648 (8.02)	19,811 (2.34)
Other cancer	15,169 (8.91)	50,951 (6.02)
COPD	8,585 (5.04)	30,762 (3.64)
Diabetes Mellitus[a]	12,357 (7.26)	42,532 (5.03)
Hypertension [b]	29,441 (17.30)	96,494 (11.41)
Cardiovascular disease	47,359 (27.83)	159,164 (18.82)
Connective tissue disease	5,556 (3.26)	17,085 (2.02)
Recent urinary tract infection or instrumentation		
Urinary tract infection, n (%)[c]	9,149 (5.38)	834 (0.10)
Urogenital or kidney procedure, n (%) [d]	13,010 (7.64)	4,374 (0.52)
Variables related to the hematuria-diagnosis only		
Type of hospital care, n (%)		
Inpatient	44,639 (26.23)	
Outpatient	116,959 (68.72)	
Emergency department	8,591 (5.05)	
Medical specialty issuing the ICD-10 diagnosis, n (%)		
Urology	102,170 (60.03)	
Nephrology	509 (0.30)	
Gynecology	3,316 (1.95)	
Other	64,194 (37.72)	
Registered type of hematuria, n (%)		
Macroscopic	42,666 (25.07)	
Microscopic	38,209 (22.45)	
Unspecified	89,314 (52.48)	
Median follow-up time, years(IQR)	6.13 (2.85-10.91)	6.38 (3.05-11.13)

ESKD: End-stage kidney disease; COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range
[a] Excl. Diabetes with renal complications
[b] Excl. Hypertensive renal disease with renal failure and hypertensive heart and renal disease with renal failure
[c] Within 1 month before index date
[d] Within 3 months before index date. Including kidney biopsy

Table 1: *Baseline characteristics of hematuria-diagnosed patients and population-based comparisons eligible for end-stage kidney disease (ESKD) analysis at baseline, Denmark 1998-2017.*

	5-year Cumulative risk[a]		10-years Cumulative risk[a]	
	% (95%CI) Hematuria	% (95%CI) Comparisons	% (95%CI) Hematuria	% (95%CI) Comparisons
All	0.42 (0.39-0.46)	0.19 (0.18-0.20)	0.73 (0.68-0.78)	0.35 (0.33-0.36)
Sex				
Male	0.52 (0.48-0.58)	0.25 (0.23-0.26)	0.92 (0.85-1.00)	0.45 (0.43-0.47)
Female	0.27 (0.23-0.32)	0.10 (0.09-0.11)	0.45 (0.39-0.51)	0.19 (0.17-0.21)
Age (years)				
<20	0.07 (0.03-0.15)	0.01 (0.00-0.03)	0.29 (0.16-0.49)	0.02 (0.01-0.04)
20-39	0.31 (0.23-0.40)	0.03 (0.02-0.04)	0.53 (0.42-0.66)	0.08 (0.06-0.11)
40-59	0.31 (0.26-0.37)	0.11 (0.10-0.13)	0.64 (0.56-0.73)	0.24 (0.22-0.26)
60-79	0.63 (0.56-0.7)	0.32 (0.30-0.34)	1.05 (0.95-1.15)	0.60 (0.57-0.64)
>79	0.31 (0.23-0.42)	0.21 (0.18-0.24)	0.35 (0.27-0.46)	0.25 (0.21-0.28)
Type of hospital care				
Inpatient	0.64 (0.56-0.73)	0.22 (0.20-0.25)	0.97 (0.87-1.09)	0.38 (0.35-0.41)
Outpatient	0.33 (0.30-0.37)	0.17 (0.16-0.19)	0.62 (0.56-0.68)	0.33 (0.31-0.35)
Emergency	0.53 (0.39-0.72)	0.19 (0.16-0.24)	0.94 (0.73-1.19)	0.35 (0.29-0.41)
Comorbidity				
Kidney disease (except cancer)	4.79 (4.28-5.35)	5.05 (4.63-5.49)	7.38 (6.67-8.14)	7.47 (6.90-8.08)
Urogenital disease (except cancer)	0.54 (0.47-0.61)	0.37 (0.33-0.42)	0.84 (0.75-0.94)	0.60 (0.54-0.66)
Urogenital or kidney cancer	0.91 (0.72-1.14)	0.50 (0.39-0.63)	1.27 (1.02-1.56)	0.78 (0.62-0.96)
Other cancer	0.62 (0.47-0.80)	0.37 (0.31-0.44)	0.84 (0.65-1.07)	0.55 (0.47-0.64)
COPD	0.69 (0.50-0.93)	0.37 (0.30-0.46)	1.07 (0.81-1.40)	0.55 (0.45-0.66)
Diabetes	1.62 (1.37-1.91)	1.05 (0.94-1.17)	2.89 (2.5-3.33)	1.84 (1.67-2.02)
Hypertension	1.10 (0.96-1.25)	0.73 (0.67-0.79)	1.87 (1.66-2.10)	1.22 (1.13-1.32)
Cardiovascular disease	0.77 (0.68-0.87)	0.49 (0.45-0.53)	1.20 (1.07-1.34)	0.79 (0.73-0.84)
Type of hematuria				
Macroscopic	0.43 (0.35-0.51)	0.20 (0.18-0.23)	0.78 (0.65-0.92)	0.37 (0.33-0.41)
Microscopic	0.29 (0.23-0.36)	0.14 (0.12-0.16)	0.50 (0.39-0.62)	0.25 (0.21-0.28)
Unspecified	0.47 (0.42-0.52)	0.20 (0.19-0.22)	0.79 (0.72-0.85)	0.37 (0.35-0.39)

CI: Confidence interval; ESKD: End-stage kidney disease; COPD: Chronic obstructive pulmonary disease

[a] Calculated as cumulative risk proportions (CIPs) treating death as a competing risk

[b] Matched with hematuria patients on age, sex and region of residency on index date

[c] Obtained within 11 years before start of follow-up

Table 2 *Cumulative risk of end-stage kidney disease (ESKD) after 5 and 10 years of follow-up among hematuria-diagnosed patients and comparison persons[b] stratified by sex, age, type of hospital care, comorbidities[c] and type of hematuria diagnosis in Denmark 1998-2018.*

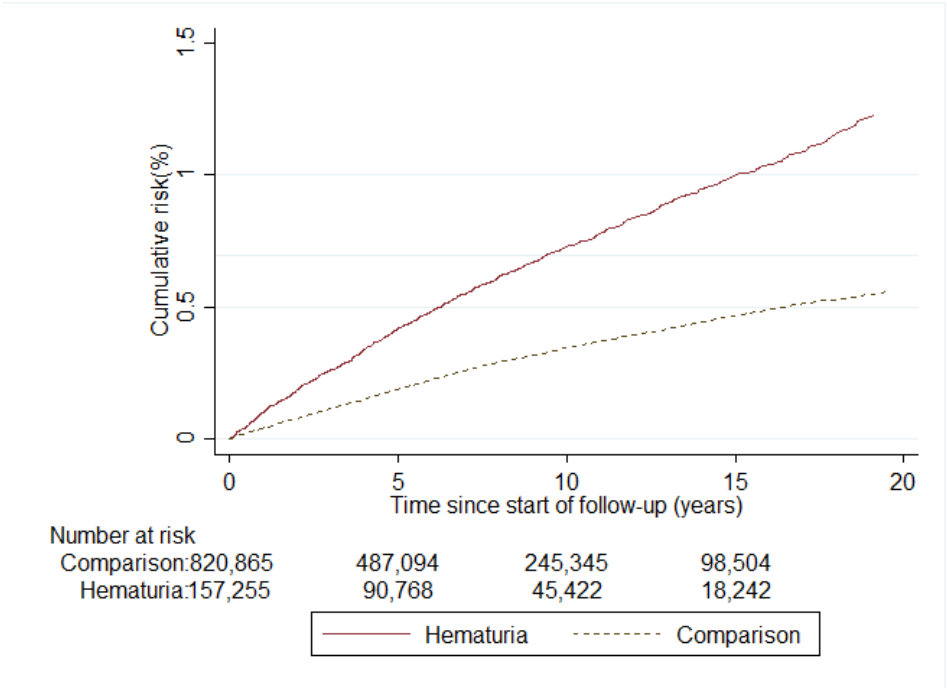
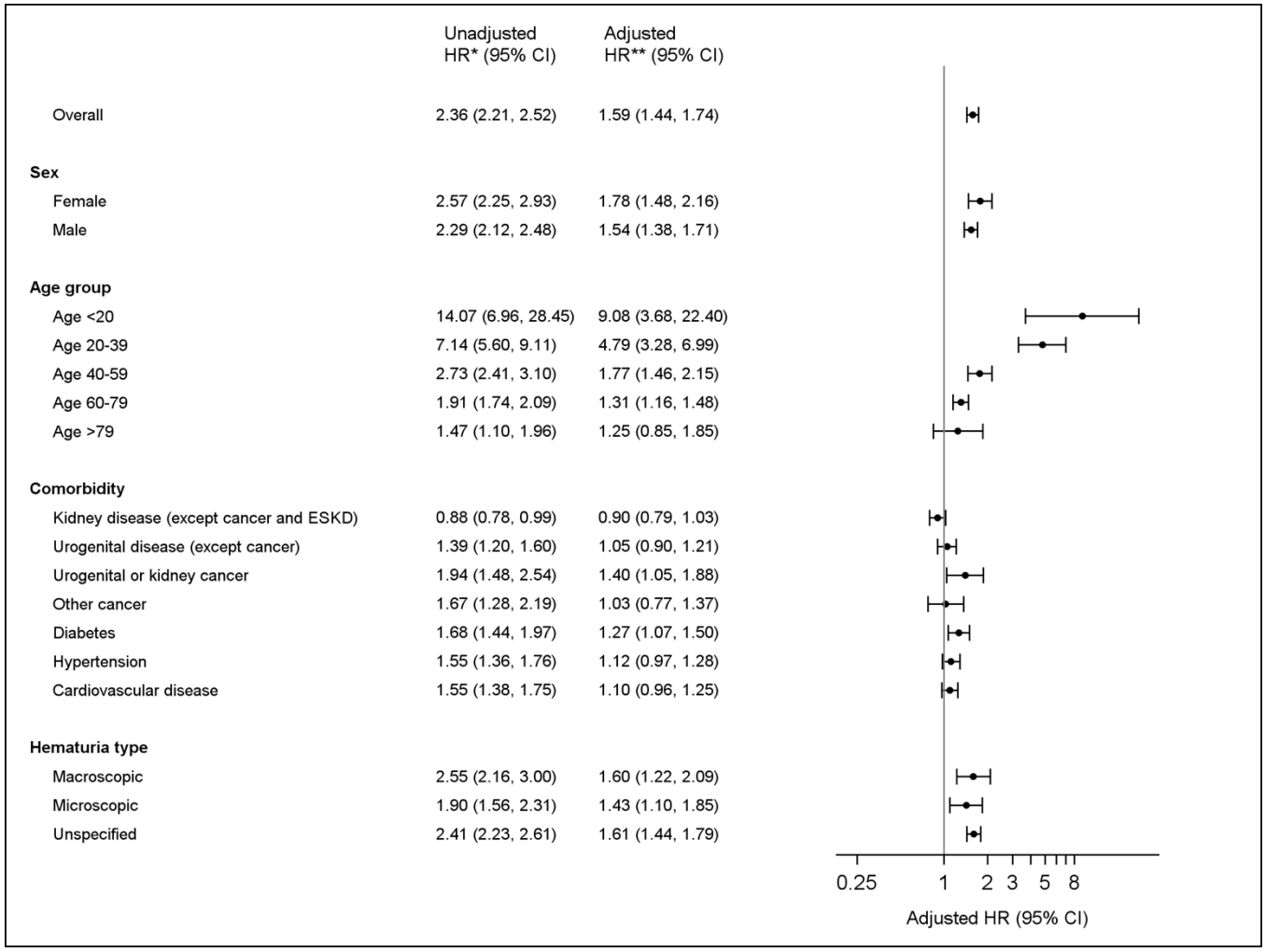


Figure 1 *Cumulative incidence of end-stage kidney disease (ESKD)*

hematuria cohort generally had higher absolute risks of ESKD across all categories compared with the comparisons, except among patients with previous kidney disease (CIP of 7.4% [95% CI: 6.7-8.1] in hematuria patients versus 7.5% [95% CI: 6.9-8.1] in comparison patients).

Relative risk of end-stage kidney disease

Patients with a hospital-based hematuria diagnosis had an increased risk of ESKD with an overall adjusted HR of 1.6 (95%CI: 1.4-1.7) compared with comparison persons. The estimated relative risk of ESKD was found slightly higher among women (adjusted HR: 1.8 [95%CI: 1.5-2.2]) than among men (HR: 1.5 [95%CI: 1.4-1.7]). Compared to comparison persons, risk of ESKD among patients with a hospital-based hematuria diagnosis gradually rose with decreasing age to a maximum adjusted HR of 9.1 [95%CI: 3.7-22.4]) in the lowest age group (Figure 2). Thus, while we found low absolute risk of ESKD as compared to all other age groups, we found a substantially increased relative risk of ESKD when comparing hematuria patients with comparison patients aged <20 year.



HR: Hazard Ratio; CI: Confidence interval; ESKD: End-stage kidney disease
* Unadjusted hazard ratios (with corresponding 95%CI) were matched for age, sex and region of residency for the following strata: sex, age group and hematuria type. Unadjusted hazard ratios (with corresponding 95%CI) are crude for the comorbidity stratas, since matching was violated.
** Hazard ratios (with corresponding 95%CI) were adjusted for sex, age and baseline comorbidities without the stratifying variable and matching variables.
***Population-based comparisons were matched on index date, age, sex and region of residency

Figure 2 *Unadjusted* and adjusted** hazard ratios (HRs) of end-stage kidney disease (ESKD) after hospital-based hematuria compared to population-based comparison*** in Denmark stratified by sex, age, comorbidities and type of hematuria diagnosis. Calculations are based on follow-up starting 1 year after the index date during 1998-2017.*

Hematuria was associated with an increased risk of ESKD regardless of type of hematuria (macroscopic hematuria: adjusted HR = 1.6, microscopic hematuria: adjusted HR=1.4, unspecified hematuria: adjusted HR=1.6) (Figure 2).

When stratified by comorbidity the association between hematuria and ESKD was generally attenuated, however still observed among patients with diabetes (adjusted HR: 1.3 [95%CI: 1.1-1.5]) and urogenital or kidney cancer (adjusted HR: 1.4 [95%CI: 1.1-1.9]).

In contrast, no clear association was found when stratified by other comorbidities and the estimated adjusted HR of 0.9 (95%CI: 0.8-1.0) for patients with previous kidney disease was even indicative of hematuria to be associated with a reduced risk ESKD (Figure 2). Excluding patients with previous or concomitant kidney disease or cancer of the kidneys or urogenital tract did not substantially change our estimates (HR: 1.6 [95%CI: 1.4-1.8]. Neither did exclusion of patients with a kidney biopsy before hematuria diagnosis (HR: 1.6 [95%CI: 1.4-1.7]).

Discussion

In this comprehensive long-term study, we found that a hospital-based diagnosis of hematuria was associated with an increased risk of ESKD. An increased risk of ESKD was observed across sex and in all types of hematuria. Even though absolute risk of ESKD was lowest in younger persons, these had the most pronounced (9-fold increased) relative risk. Of note, a hospital hematuria-diagnosis was a marker of ESKD risk in all ages even after adjusting for important risk factors for ESKD such as hypertension, diabetes mellitus and CVD.

Confirmation and new aspects of ESKD risk

No previous study has estimated the risk of ESKD in hospital-diagnosed hematuria patients compared with that of the background population in a European setting. Few previous mass screening studies have estimated the risk of ESKD or CKD in patients with urinalysis-verified isolated hematuria who had no apparent underlying cause of hematuria (ie. denoted asymptomatic hematuria in the literature) compared with patients with normal urinalysis[5-7]. The magnitude of the overall association we found between hematuria and ESKD (adjusted HR 1.6 [95%CI: 1.4-1.7]) were comparable to the long-term risk of CKD (adjusted HR 1.5 [95%CI: 1.1–1.9]) recently reported by Kim et al[7], despite CKD being considered a less advanced kidney function impairment in the trajectory of ESKD development.

Our findings of a high relative risk of ESKD in hematuria patients in the young age stratum corroborate the earlier findings by Vivante et al who found dipstick hematuria to be associated with an 18.5-fold increased risk of ESKD in the young population of Israeli adolescents[5]. Still, these young persons have a low absolute risk of ESKD.

Our finding that a hematuria diagnosis was associated with an increased risk of ESKD across all ages was consistent with that of Iseki et. al[8]. In great correspondence with our unadjusted estimate (HR 2.7 95%CI 2.2-2.5), they observed that patients with dipstick hematuria were associated with a 2.3-fold increased risk of developing ESKD compared with controls with normal urinalysis. Our study therefore, extends these previous findings by being able to take previous comorbidity and the underlying cause for hematuria into account.

Our nationwide population-based study also adds to the previous studies mainly conducted within selected sub-populations using either mass screening or volunteer-recruitment in a community-based cohort[5-7], with all but one conducted in East Asia. Considering aetiologies responsible for CKD and ESKD development, a clear geographic prevalence variation has been described[9, 10]. With IgA nephropathy being a prevalent cause of ESKD in East Asian populations[9], whereas diabetic nephropathy constitutes the primary single cause of ESKD in the Western part of the world[10], there may be limitations to the extrapolation to western populations of the previously reported results. Lastly, given the strong established correlation between macroscopic or high degree microscopic hematuria and urologic cancer risk[16, 17], most previous studies have focused on microscopic hematuria as a risk factor for ESKD. We found an increased risk of ESKD in hematuria-diagnosed patients irrespective of type of hematuria.

Hematuria as a marker of ESKD risk was not as evident in the elderly

Age and particularly functional age is a well-described risk factor for ESKD[18], however we found a slightly lower absolute risk of ESKD in the elderly (>79 years old). This may reflect a more conservative approach instead of dialysis therapy towards elderly patients with advanced CKD. As compared to our overall results, the magnitude of the association we found between hematuria and ESKD risk was somewhat lower among the elderly. Older age seems to reduce the significance of hematuria as a marker of ESKD risk. This could possibly be explained by an increased prevalence of multiple competing causes of ESKD in the older age group and furthermore, by the elderly patients being more likely to be excluded from the present study due to higher risk of urogenital cancers [17].

The impact of previous kidney disease on ESKD risk

We found no association between a hematuria diagnosis and ESKD risk in patients with a history urogenital disease nor among patients with a history of kidney disease. In contrast, our results of patients with a history of kidney disease even suggested a reduced risk of ESKD associated with a hematuria diagnosis. Recent evidence has pointed to the negative implications of hematuria on the progression of chronic kidney disease to ESKD[19, 20]. We speculate that this divergent finding in patients with a history of kidney disease may be explained by the diversity of aetiologies covered in the group of kidney diseases, hence reflecting different impact on the prognostic value of a hematuria diagnosis. Whereas most previous studies excluded patients with a history of kidney disease[5-7], our observations of no increased relative risk of ESKD however, is of great importance.

Strengths & Limitations

Our study used a population-based design and had a nationwide coverage in a setting with universal access to healthcare. This approach ensured a minimal risk of selection bias and provided a large sample-size of more than of 1,015,000 subjects with virtually complete follow-up for more than 20 years. Additionally, the high quality prospectively collected individual-level data enabled us to link registries and to take a range of potential confounders into account.

Nonetheless, our study has limitations. Data validity is generally high in the DNPR [13], yet the hematuria diagnosis has not formally been validated. However, hematuria was likely predominantly coded if initial diagnostic work-up ruled out an apparent underlying cause. We therefore expect our study population to consist of hematuria patients with no apparent underlying condition. Excluding patients with previous or concurrent kidney and urogenital comorbidity did not reveal altered risk of EKSD which supported our expectations. However, we cannot fully rule out inclusion of few hematuria cases where the underlying condition triggering the hematuria may have been prevalent at hematuria diagnosis.

Likewise, the diagnosis of ESKD was not directly validated. A Danish study, however validated the Danish National registry on dialysis and transplantation against DNPR and found that of 3020 patients registered in the National Patient Registry as incident chronic RRT patients, 97.2% were found in NRDT[21]. Furthermore, treated ESKD is an advanced

clinical outcome and correct coding is subject to financial reimbursement by the Danish national health service. We therefore, expect the coding of ESKD to have high validity and its detection and coding are unlikely to be influenced by any previously diagnosed hematuria.

We did not have access to clinical data on measured hypertension, symptoms accompanying hematuria (e.g. irritative bladder symptoms), lifestyle-factors (BMI, smoking) and biochemical findings (e.g. proteinuria, serum creatinine). Previous studies have demonstrated obesity, hypertension and smoking to be important risk factors for ESKD[8, 22]. We used diagnoses of COPD as a proxy for smoking for confounder adjustment however, we cannot rule out the possibility that unmeasured and residual confounding by these factors remain. Additional stratified clinical information of hematuria-diagnosed patients is needed to further distinguish high-risk subgroups for differential risk assessment of ESKD.

In conclusion, we showed that a hospital-based hematuria diagnosis in patients with no apparent cause of hematuria may be a risk marker of future ESKD. The increased ESKD risk was found across all ages with the most marked relative risk increase among young patients. Despite low incidences of ESKD, it is a serious outcome requiring costly renal replacement therapy. Our findings suggest, that the seemingly insignificant hospital-related hematuria diagnosis is related to a significantly increased risk of future kidney failure and should be appreciated in the management of hematuria-diagnosed patients.

Conflict of interests

Fogh, Vestergaard, Christiansen, Pedersen, Nørgaard report employment at the Department of Clinical Epidemiology at Aarhus University Hospital, which is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these are related to this study. Dr. Nitsch has received research grants from GlaxoSmithKline to two unrelated studies.

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