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Epidemiology of Acute Kidney Injury in Denmark

Population-based studies of occurrence and prognosis

PhD dissertation

Simon Kok Jensen

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Supervisors

Christian Fynbo Christiansen, MD, PhD, Professor, Consultant (Main supervisor)

Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

Uffe Heide-Jørgensen, MSc, PhD, Part-time Lecturer, Statistician (Co-supervisor)

Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

Henrik Gammelager, MD, PhD, Pre-graduate education officer, Senior Registrar (Co-supervisor)

Department of Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark

Henrik Birn, MD, PhD, DMSc, Professor, Consultant (Co-supervisor)

Department of Biomedicine, Aarhus University, Aarhus, Denmark

Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark

Collaborators

Søren Viborg Vestergaard, MD, PhD, Resident

Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark

Dorothea Nitsch, MD, MSc, Professor, Honorary Consultant

Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Simon Sawhney, MD, PhD, Senior Lecturer, Consultant

Aberdeen Centre for Health Data Science, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, Scotland

NHS Grampian, Aberdeen, Scotland

Søren Paaske Johnsen, MD, PhD, Professor, Consultant

Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Henrik Toft Sørensen, MD, PhD, DMSc, DSc, Professor, Consultant and Chair

Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

Thomas Bøjer Rasmussen, MSc, Statistician

Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

Bjarke Hejlskov Jacobsen, MSc, Statistician

Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

Assessment committee

Per Ramløv Ivarsen, MD, PhD, Professor, Consultant (Chairman of the committee)

Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark

Marlies Ostermann MD, PhD, Honorary Senior Lecturer, Consultant

Department of Critical Care, King's College London, London, United Kingdom

Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

Lisbet Brandi, MD, PhD, DMSc, Associate Professor, Head Consultant

Institute of Clinical Medicine, Copenhagen University, Copenhagen, Denmark

Department of Endocrinology and Nephrology, Nordsjællands Hospital, Hillerød, Denmark

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List of papers

This dissertation is based on the following four studies, which will be referred to by their Roman numerals (I-IV). The studies are attached in the corresponding appendices, I-IV.

I. **Routine Clinical Care Creatinine Data in Denmark - An Epidemiological Resource for Nationwide Population-Based Studies of Kidney Disease.**
Jensen SK, Heide-Jørgensen U, Vestergaard SV, Sørensen HT, Christiansen CF. Clin Epidemiol. 2022 Nov 22;14:1415-1426. doi: 10.2147/CLEP.S380840.

II. **Kidney function before and after acute kidney injury: a nationwide population-based cohort study.**
Jensen SK, Heide-Jørgensen U, Vestergaard SV, Gammelager H, Birn H, Nitsch D, Christiansen CF. Clin Kidney J. 2022 Nov 18;16(3):484-493. doi: 10.1093/ckj/sfac247.

III. **Regional variation in incidence and prognosis of acute kidney injury in Denmark: a population-based cohort study**.
Jensen SK, Rasmussen TB, Jacobsen BH, Heide-Jørgensen U, Sawhney S, Gammelager H, Birn H, Johnsen SP, Christiansen CF. *Submitted.*

IV. **Acute kidney injury duration and 20-year risks of chronic kidney disease and cardiovascular disease: a population-based cohort study.**
Jensen SK, Heide-Jørgensen U, Gammelager H, Birn H, Christiansen CF. *In preparation.*

Abbreviations

aHR	Adjusted hazard ratio
ADQI	Acute Dialysis Quality Initiative
AKD	Acute kidney disease
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARF	Acute renal failure
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRS	Civil Registration System
CVD	Cardiovascular disease
DNPR	Danish National Patient Registry
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
HR	Hazard ratio
ICD	International Classification of Disease
ICU	Intensive care unit
IQR	interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
LABKA	Clinical Laboratory Information System Research Database
MACE	Major atherosclerotic cardiovascular event
MAKE	Major adverse kidney event
MDRD	Modification of Diet in Renal Disease
MeSH	Medical Subject Headings
NHSR	National Health Service Registry
NPR	National Prescription Registry
pCr	Plasma creatinine
PPV	Positive predictive value
RIFLE	Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease
RLRR	Register of Laboratory Results for Research
sCr	Serum creatinine
SNOMED	Systemized Nomenclature of Medicine
UO	Urine output

Contents

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1. Introduction

Acute kidney injury (AKI) has been estimated to affect approximately 13 million individuals worldwide annually and is associated with increased morbidity and mortality.[1,2] In the United States alone, the derived annual costs of AKI have been estimated to be in excess of 9 billion US dollars.[3] Changes in demographics, including population aging and rise in conditions associated with AKI, are expected to cause an increase in the incidence and the related costs of AKI in the coming decades.[3-6] Owing to the poor prognosis, high associated costs, and increasing incidence, AKI is considered a global health problem.[7-10]

Despite the evident clinical importance and substantial derived costs, research in AKI has been impeded by changing definitions and unavailability of laboratory-based information on kidney function. The collaborative development of consensus criteria for AKI and increasing availability of clinical care serum creatinine (sCr) data have been central in moving towards a better understanding of the condition.[1] Based on this, the current dissertation aims at examining the occurrence and prognosis of AKI in a population-based setting. This encompasses describing the availability of population-based creatinine data in Denmark (Study I), changes in kidney function associated with AKI (Study II), regional variation in AKI incidence and prognosis (Study III), and associations between AKI duration and chronic kidney disease (CKD) and cardiovascular disease (CVD) (Study IV).

The dissertation consists of 12 chapters. The following chapter provides the background for the dissertation, including a presentation of the current knowledge about AKI, a review of the literature pertaining to each of the four studies included in the dissertation, and current knowledge gaps. Chapters 3, 4, and 5 describe the hypotheses and aims, key methodological aspects, and the main findings of the included studies. In chapter 6, the main findings are considered in the context of the current literature and key methodological considerations are presented. Chapters 7 and 8 provide the overall conclusions and future perspectives. The final chapters include summaries in English and Danish, references, and appendices including the full versions of the research papers for each of the four studies.

2. Background

2.1 Definitions of acute kidney injury

The first recordings of acutely impaired kidney function date back to ancient Greece and include an observation of capillary hemorrhage and destruction of kidney parenchyma due to external damage by Hippocrates.[11] In the time of modern medicine, Heberden provided the first clinical description of acutely impaired kidney function in "Commentaries on the history and cure of diseases" from 1802.[12] Here, he described a condition with complete suppression of urine production, which was generally deadly by the sixth or seventh day.[12] However, little focus was given to the condition until the publication of "Crush injuries with impairment of renal function" in 1941 by Bywaters and Beall, who reported on four patient cases observed during the bombing of London in World War II.[13] This publication embarked a renewed interest in the field of acutely impaired kidney function leading to the introduction of the term acute renal failure (ARF) by Smith in 1951.[14] Yet, studies performed before 2000 used a wide variety of ARF definitions impeding comparisons across studies.[15] With the purpose of defining the first consensus-based definition for ARF, a large network of international experts in nephrology and intensive care medicine formed the Acute Dialysis Quality Initiative (ADQI) workgroup in 2002.[16] The ADQI workgroup published the Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease (RIFLE) definition for ARF in 2004.[16] Here ARF was defined as: 1) an increase in sCr of >1.5 times baseline; 2) a >25% decrease in estimated glomerular filtration rate (eGFR) from baseline; or 3) an urine output (UO) <0.5 ml/kg/h for six hours or longer. In addition, the RIFLE definition included three levels of kidney function impairment (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function) based on changes in eGFR, sCr, and/or UO and two levels of clinical outcomes (Loss of kidney function, and End-stage kidney disease) based on the duration of kidney function impairment (Table 1).

After the RIFLE definition was published, studies showed that changes in sCr below the threshold for ARF had prognostic importance.[17,18] This led to a modification of the RIFLE definition by the Acute Kidney Injury Network (AKIN) in 2007.[19] In comparison with the RIFLE definition, the modifications provided in the AKIN definition included that: 1) AKI could be defined by an absolute increase in sCr of ≥0.3 mg/dl (≥26.5 µmol/l); 2) the eGFR criterion was removed and changes in sCr were required occur within 48 hours; 3) the levels of kidney function impairment (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function) were replaced by stages 1-3 and the two levels of clinical outcomes (Loss of kidney function and End-stage kidney disease) were removed from the staging system; and 4) AKI accompanied by acute KRT was by definition stage 3 (Table 1).[19]

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group published the current consensus definition for AKI.[1] This definition integrated elements from both the RIFLE and AKIN definitions, as it had been established that both definitions missed patients with a similar prognosis as those identified.[20] While retaining the absolute increase in sCr of ≥0.3 mg/dl within 48 hours from the AKIN definition, the KDIGO definition does not require the relative increase in sCr of ≥1.5 times baseline to occur within 48 hours; instead, the increase should be known or presumed to have occurred within seven days (Table 1).

The RIFLE, AKIN, and KDIGO definitions share the conception of AKI as a broad clinical syndrome ranging from a mild change in markers of kidney function to an injury requiring kidney replacement therapy (KRT) and encompassing both primary kidney conditions and conditions outside the kidneys.[1] Thus, the AKI concept is intended to enable early identification of patients and allow for timely interventions. During the past decade, great efforts have been made to develop new biomarkers that support the identification of patients at high risk of AKI.[21,22] With the recently announced update of the 2012 KDIGO guideline, it will be interesting to see if more of these will be recommended for use in clinical practice.[23]

Table 1. Classification of acute kidney injury

Classification[a]	RIFLE[16]	AKIN[19]	KDIGO[1]
Risk / stage 1	sCr increase of 1.5-1.9 times baseline[b] *or* GFR decrease of >25% from baseline *or* UO <0.5 ml/kg/h ≥6 hours	sCr increase of 1.5-2.0 times baseline[c] *or* sCr increase of ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours *or* UO <0.5 ml/kg/h for >6 hours	sCr increase of 1.5–1.9 times baseline[d] *or* sCr increase of ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours *or* UO <0.5 ml/kg/h for 6-12 hours
Injury / stage 2	sCr increase of 2.0-3.0 times baseline[b] *or* GFR decrease of >50% from baseline *or* UO <0.5 ml/kg/h for ≥12 hours	sCr increase of >2.0-3.0 times baseline[c] *or* UO <0.5 ml/kg/h for >12 hours	sCr increase of 2.0–2.9 times baseline[d] *or* UO <0.5 ml/kg/h for ≥12 hours
Failure / stage 3	sCr increase of ≥3.0 times baseline[b] *or* sCr ≥4.0 mg/dl (≥354 µmol/l) with an acute increase of ≥0.5 mg/dl (44 µmol/l) *or* GFR decrease of >75% from baseline *or* UO <0.3 ml/kg/h for ≥24 hours *or* anuria for ≥12 hours	sCr increase of >3.0 times baseline[c] *or* sCr ≥4.0 mg/dl (≥354 µmol/l) with an acute increase of ≥0.5 mg/dl (≥44 µmol/l) *or* Initiation of KRT *or* UO <0.3 ml/kg/h for ≥24 hours *or* anuria for ≥12 hours	sCr increase of ≥3.0 times baseline[d] *or* sCr ≥4.0 mg/dl (≥354 µmol/l) when fulfilling another criterion for AKI *or* Initiation of KRT *or* In patients <18 years, decrease in eGFR to <35 ml/min/1.73 m^2 *or* UO <0.3 ml/kg/h for ≥24 hours *or* anuria for ≥12 hours
Loss	Need for KRT for >4 weeks	Not defined	Not defined
ESKD	Need for KRT for >3 months	Not defined	Not defined

Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury[1] and Gammelager[24].

[a]Stage is based on the most severe of the sCr, eGFR, or UO criteria.

[b]Baseline specification is not provided. A theoretical baseline can be estimated using the MDRD formula assuming a normal GFR of approximately 75–100 ml/min/1.73 m^2.

[c]A sCr test within 48 hours.

[d]The baseline should reflect the sCr level before AKI. In patients without CKD this could be a test within a year if the change in sCr is known or presumed to have occurred within the prior seven days.

Abbreviations: AKIN, Acute Kidney Injury Network; CKD; chronic kidney disease; ESKD, End-stage kidney disease, GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcome; KRT, kidney replacement therapy; MDRD, Modification of Diet in Renal Disease; RIFLE, Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease; sCr, serum creatinine; UO, urine output.

2.2 The epidemiology of acute kidney injury

AKI has a reported incidence of approximately 2,000-3,000 cases per million person-years in the general population and occurs in one out of five hospitalized patients.[25-27] The incidence of AKI has increased in recent decades, which is likely to reflect an increase in predisposing conditions such as CVD, CKD, and diabetes, in addition to population aging and increased awareness of the condition.[6,9,28-37]

Traditionally, AKI has been subdivided into prerenal, renal/intrinsic, and postrenal based on the location of the causing insult.[38] Prerenal causes of AKI include sepsis, hemorrhage, dehydration, and surgery, while renal causes include specific kidney diseases, e.g., vascular, tubular, glomerular, and interstitial diseases, and postrenal causes include obstruction of the urinary tract.[38] While this provides a framework for understanding the mechanisms underlying AKI, the clinical and prognostic utilization of the categorization has been questioned.[39-41] First, prerenal AKI may cause structural changes and thereby transition to renal AKI. Furthermore, differentiating between prerenal AKI and renal AKI caused by prerenal AKI has few implications for treatment.[39,42] Therefore, it has been argued to supplement the characterization of AKI by including factors such as the specific cause, the clinical setting, the severity and duration of AKI, and baseline kidney function.[42,43]

AKI is associated with an increased mortality and more than 20% of hospitalized patients with AKI die during the hospitalization.[27,44,45] Common short-term complications of AKI include brain, heart, lung, and liver dysfunction.[46] Moreover, patients surviving the acute phase of AKI have increased risks of developing CKD[47-49] and CVDs including hypertension,[50] ischemic heart disease,[45,51,52] heart failure,[52-54] and stroke.[52] Even patients with recovery of eGFR after AKI have an increased risk of developing CKD and the risk of kidney failure with replacement therapy has been shown to remain elevated for up to 10 years after AKI.[55-60] Factors associated with a worse prognosis include advanced age, higher AKI stage, low baseline eGFR, and comorbidities such as diabetes, hypertension, and heart failure.[4,48,61] In addition, the duration of AKI may affect the prognosis, which is discussed further in section 2.6.4.

2.3 Standard of care for acute kidney injury

The standard of care for AKI includes prevention, early detection, treatment, and follow-up.[1,62,63] Primary prevention would involve reducing the occurrence of predisposing conditions, including CVD, CKD, and diabetes, on a population level.[64] However, while the age-standardized prevalence of CVD and CKD may have plateaued, the crude prevalence of CKD, CVD, and diabetes continues to increase due to an aging population.[28,35,36]

The increasing prevalence of predisposing conditions underlines the potential for secondary prevention by the identification of patients at risk and early detection of AKI.[64] Identification of patients at risk of AKI may be aided by prediction models and novel biomarkers.[63,65,66] However, while such risk assessment tools have been proven to be able to identify patients at high risk and even reduce AKI incidence, most tools have been developed based on specific patient populations, e.g., patients undergoing cardiac surgery, and need to be validated in other settings.[63,67-71]

Identification of AKI can be aided by electronic warning systems such as the National Health Service AKI warning system in England.[72] The implementation of the automatic alert has been associated with increased detection of and recovery after AKI.[73] Furthermore, integration between electronic warning systems and AKI-directed treatment initiatives has been shown to be associated with a reduction in progression of AKI and mortality after AKI.[74]

Apart from managing the underlying cause, treatment of AKI includes close monitoring, discontinuation of potentially nephrotoxic drugs, optimization of hemodynamic status, avoidance of hypoglycemia, KRT, and medical management of associated complications such as hyperkaliemia, acidosis, and fluid overload.[62,63] These actions, often collectively referred to as AKI care bundles, have been reported to be associated with decreased mortality and are starting to be systematically implemented in high-risk settings such as cardiac surgery.[74-77]

Following the initial phase, tertiary prevention by clinical and laboratory follow-up tailored to the severity of AKI is recommended.[1] Nephrologist follow-up has been shown to improve survival among patients with severe AKI but is infrequently performed.[78,79]

2.4 Acute kidney injury duration and acute kidney disease

The ADQI workgroup has proposed categories for the duration of AKI with the aim of providing a shared framework for studying the association between AKI duration and prognosis.[80] According to this classification, AKI is defined as rapid reversal AKI if the duration is <48 hours, as persistent AKI if the duration is two to seven days, and as acute kidney disease (AKD) if the duration is beyond seven days. Furthermore, recovery of kidney function should be present for ≥48 hours before one AKI episode can be differentiated from another AKI episode.[80] However, broadly agreed definitions for the transition from an acute to a subacute kidney condition are missing. The KDIGO workgroup has proposed AKD to cover both AKI and periods of <3 months with eGFR <60 ml/min/1.73 m^2, a decrease in eGFR of ≥35%, or an increase in sCr of >50%.[1,81] In contrast, the ADQI definition of AKD does not include AKI but strictly covers conditions fulfilling the AKI definition for seven days or longer.[80]

2.5 Defining acute kidney injury in studies using routinely collected healthcare data

A broad range of AKI definitions and implementations have been applied in studies using routinely collected healthcare data.[82] AKI episodes during hospitalization can be recorded in medical databases according to the International Classification of Diseases 9th (ICD-9) or 10th edition (ICD-10). In research settings without access to sCr or OU data, this is the only way to identify AKI. The specificity of hospital-recorded AKI diagnoses has been reported to be 95%-98%; however, the sensitivity is low and AKI diagnoses may only capture one-third of AKI episodes identified by changes in sCr.[83-86] In addition, the validity of diagnoses codes can be affected by variations in coding quality across healthcare settings, changes in diagnostic criteria and coding practices over time, and patient characteristics such as age.[86,87]

When sCr and UO data are available, direct application of the KDIGO criteria is preferable as both measures are associated with risks of kidney failure and death.[1,88] However, valid measures of hourly UO are rarely available outside the intensive care unit (ICU) and the UO criterion is therefore seldom applied in studies outside this setting.[89,90] In contrast, sCr is often measured regularly in routine clinical care. Creatinine is a by-product of muscle metabolism with a production proportional to the total muscle mass.[38,91] It is freely filtered in the renal glomerulus and secreted in the proximal tubules, which makes it an incomplete marker of glomerular filtration rate (GFR).[91] Furthermore, changes in sCr may reflect changes in dietary protein intake or muscle mass, which are common during acute illness. However, as the level of sCr varies inversely with GFR, sCr is used as an endogenous marker of GFR with these limitations.[43,92] In Denmark, creatinine is measured as plasma creatinine (pCr), which is equivalent to sCr.[93,94]

Application of the KDIGO sCr criteria of a relative increase of ≥1.5 known to have occurred within the prior seven days, or an absolute increase of ≥26.5 µmol/l within 48 hours is intuitively straightforward when sCr tests within the specified periods are available. However, this is often only the case in situations with planned surgery or other planned medical procedures. For patients with a presumed acute increase in sCr, who did not have a sCr test in the past week for comparison, several definitions of baseline sCr have been suggested.[95-97] Approaches for defining baseline sCr include using the most recent sCr test,[97-99] the median sCr level,[100,101] or the mean sCr level,[102] within the past 8-365 days.[96] A recent study showed that while the absence of a baseline definition dramatically reduced the AKI population, the use of different baseline definitions yielded similar populations.[103] Furthermore, using the median sCr level based on the past year was recently recommended by a Delphi panel of researchers working with AKI.[90] Finally, a sCr test may not have been performed within the past year. In this situation, strategies to estimate the baseline sCr level include simple imputation,[104] multiple imputation,[104] or using the first or the last sCr test during

hospitalization.[105-107] However, these methods all come with a non-negligible risk of misclassification and most studies exclude patients without an actual baseline test.[90,97,104,108]

2.6 Literature review for the included studies

Four independent literature reviews were performed to examine the existing knowledge for each of the studies included in the dissertation. Specifically, searches were done to assess the current literature on population-based databases with creatinine data (Study I), the association between AKI and changes in kidney function (Study II), regional variation in incidence and prognosis of AKI (Study III), and the associations between AKI duration and CKD and CVD (Study IV).

The literature searches were performed using MEDLINE (PubMed) with a combination of Medical Subject Headings (MeSH) terms and free-text with the Boolean operators "AND"/"OR". Searches were restricted to studies written in English, Danish, Swedish, or Norwegian and were last updated in February 2023.

After searching the MEDLINE database, an initial screening of headlines and abstracts was performed and relevant articles were retrieved. Next, the eligibility of full-text articles was evaluated by considering data quality, choice of analyses, and risk of bias. Last, the reference lists of included articles were screened for additional relevant studies not identified by the literature search. For Study IV, we restricted to studies evaluating the associations between AKI duration and CKD and CVD using more than one category of AKI duration. The included studies are summarized in Tables 2-5 and the main findings are presented in synthesis below.

2.6.1 Population-based databases with creatinine data (Study I)

sCr data are increasingly used to study AKI.[90] Even so, only a few studies that described databases with population-based sCr data were identified in the literature search (Table 2).[109-112] These comprised two Danish, one Swedish, and one Canadian study. The studies by Kampmann et al.[109] and Henriksen et al.[110] covered pCr data in two geographical areas of Denmark. Kampmann et al.[109] described pCr data from a defined geographical area in the Region of Southern Denmark during 2007-2013. The database covered 857,854 adult residents of whom 669,929 had a pCr test, which was equivalent to a population coverage (i.e., the percentage of the population with a pCr test) of 78% in the study period. Similarly, Henriksen et al.[110] examined pCr data from Funen and the surrounding islands in Denmark covering 693,843 residents during 2000-2015. They reported a population coverage of 66% in the study period.

Runesson et al.[111] examined sCr data in Stockholm County covering 1,706,529 adult residents during 2006-2011. Similar to the Danish studies, they found a population coverage of 66% during the six-year period with around one-third of individuals having an annual sCr test. Finally, the study by Garg et al.[112] included sCr data from both private and hospital-based laboratories in Eastern Ontario covering 1,090,000 adult residents from 1 September 1999 to 1 September 2000. The database included sCr data from both primary care and hospitals, but only tests from primary care were included in the analyses. Nonetheless, they reported a population coverage of 32% during a one-year period.

All studies reported a higher proportion of females among tested individuals than in the general population. Moreover, most studies found an increasing coverage with advancing age,[110-112] which in the two Danish studies was reflected by a higher median age of tested individuals than in the general population.[109,110]

Table 2. Summary of the existing literature for Study I.

Study I: Population-based databases with creatinine data			
Author, journal, year	**Design, setting, data sources, period**	**Study population, creatinine test setting**	**Results**
Kampmann et al.,[109] Clinical Epidemiology, 2021	- Cohort study - Denmark - 17 of 22 municipalities in the Region of Southern Denmark - Local laboratory databases and nationwide registries - 2007-2013	- Residents ≥18 years (*n* = 857,854) - pCr tests from primary care and hospitals	- 7,996,882 pCr tests from 669,929 individuals during a seven-year period - 78% of residents had a pCr test in the study period - 54% of individuals in the pCr-tested cohort were females. The median age was 51 years - 50% of individuals in the general population were females. The median age was 45 years
Henriksen et al.,[110] Basic & Clinical Pharmacology & Toxicology, 2019	- Cohort study - Denmark - Funen and surrounding islands - The laboratory database of Odense University Hospital and nationwide registries - 2000-2015	- Residents (*n* = 693,843) - pCr tests from primary care and hospitals	- 7,742,124 sCr tests from 460,365 individuals during a 16-year period - 66% of residents had a pCr test in the study period - The annual proportion of individuals with a pCr test increased from 20% in 2000 to 42% in 2015 - 53% of individuals in the pCr-tested cohort were females. The median age at the end of the study period was 53 years (IQR, 32-70) - 50% of individuals in the general population were females. The median age was 43 years (IQR, 23-65) - Coverage increased with advancing age
Runesson et al.,[111] Clinical Kidney Journal, 2016	- Cohort study - Sweden - Stockholm County - Local laboratory databases and national registries - 2006-2011	- Residents ≥18 years (*n* = 1,706,259) - sCr tests from primary care and hospitals	- 1,118,507 individuals had a sCr test during a six-year period - 66% of residents had a pCr test in the study period and around one-third of the population was tested annually - 54% of individuals in the sCr-tested cohort were females - Coverage increased with advancing age
Garg et al.,[112] Journal of the American Society of Nephrology, 2005	- Cohort study - Canada - Eastern Ontario - Private and hospital-based laboratory databases, regional medical databases, and Canadian census data - 1999-2000	- Residents ≥18 years (*n* = 1,090,000) - sCr tests from primary care and hospitals (only tests from primary care were described)	- 566,870 primary care sCr tests from 346,513 individuals during a one-year period - 32% of residents had a pCr test during the year of study - 57% of individuals in the sCr-tested cohort were females. The median age was 54 years (IQR, 41-69) - Coverage increased with advancing age
MEDLINE search query: ("creatini*"[tiab]) AND ("laborator*"[tiab]) AND (("register*"[tiab]) OR ("registry*"[tiab]) OR ("databas*"[tiab])) Hits: 684 Last updated: 14 February 2023			

Abbreviations: IQR, interquartile range; pCr, plasma creatinine, sCr, serum creatinine.

2.6.2 Kidney function before and after acute kidney injury (Study II)

AKI is consistently associated with an increased risk of incident CKD and an increased risk of kidney failure with replacement therapy among individuals with prevalent CKD.[48,58,113,114] Conceptually, AKI could be linked with CKD and kidney failure with replacement therapy through an unrecovered drop in eGFR level, an accelerated rate of eGFR decline (i.e., a steeper eGFR slope), or a combination of both (Figure 1).

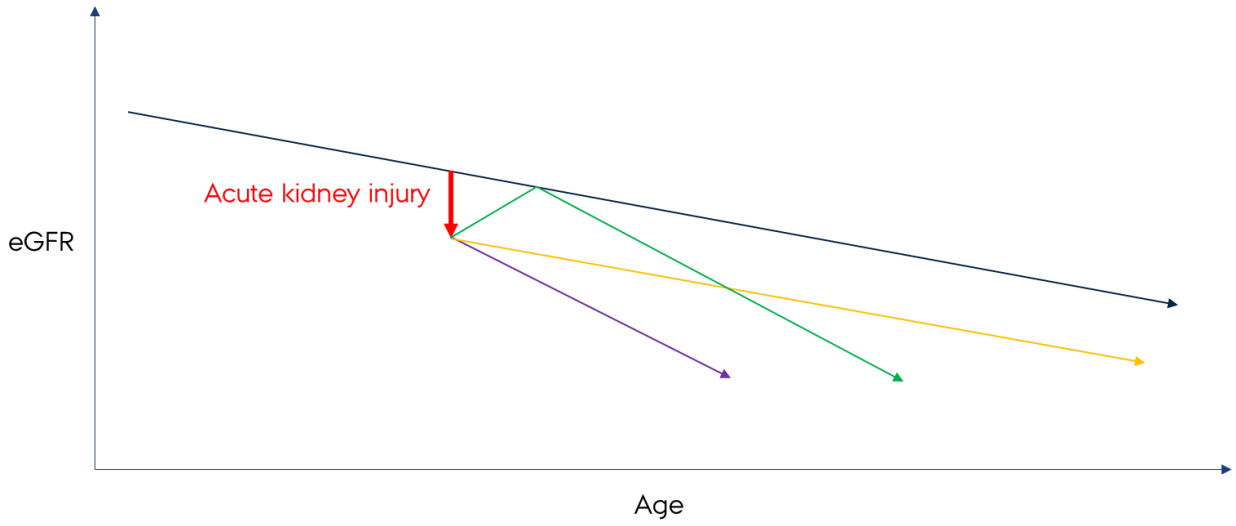

Figure 1. Conceptual model of the association between AKI and changes in eGFR. Black, normal age-related decline in eGFR. Red, AKI. Green, recovery of eGFR to the level before AKI followed by an accelerated rate of eGFR decline. Orange, non-recovery of eGFR level after AKI followed by the same rate of eGFR decline as before AKI. Purple, non-recovery of eGFR level after AKI followed by an accelerated rate of eGFR decline. Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

Studies describing the association between AKI and changes in kidney function are presented in Table 3.[115-121] Most studies were conducted in specific patient populations, including patients with CKD,[117-119] patients undergoing coronary angiography,[120] and patients in intensive care.[115] Additionally, most studies were limited by small patient populations (<1000 patients with AKI).[115-120] Only one study included a general unselected cohort; however, this study identified AKI using diagnosis codes and only reported relative changes in eGFR level.[121]

Various approaches were applied to define changes in eGFR in relation to AKI. While most studies reported changes in both eGFR level and eGFR slope,[115-117,119,120] others reported only one or the other.[118,121] Moreover, the term "change in eGFR level" was used to describe both the difference in eGFR level at the time of AKI (i.e., derived from a statistical model extrapolating eGFR levels to the time of AKI using eGFR trajectories before and after AKI),[117] and the difference in eGFR levels from before or at admission and at or after discharge.[115,119-121]

The magnitude and direction of the reported changes in eGFR from before to after AKI varied substantially. In general, studies reported a drop in eGFR level following AKI.[115,119-121] However, a stable or higher eGFR level after AKI was also reported.[117,121] Studies examining changes in the rate of eGFR decline generally reported a higher rate of eGFR decline after AKI.[117,118,120] However, as for changes in eGFR level, some studies reported similar rates of eGFR decline before and after AKI[121] or even a lower rate of eGFR decline after AKI.[119]

Table 3. Summary of the existing literature for Study II.

Study II: Kidney function before and after acute kidney injury			
Author, journal, year	**Design, setting, data sources, period**	**Study population, exposure, outcome, analysis**	**Results**
Haines et al.,[115] Scientific Reports, 2021	- Cohort study - UK - Single center - Electronic medical records, routinely collected laboratory results, and national registries - 2004-2008	- ICU patients with eGFR data during follow-up (*n* = 1,301) - Exposure: AKI (*n* = 659) - Outcome: eGFR level and short-term (0-6 months) and long-term (0.5-7 years) rates of eGFR decline - Analysis: Linear mixed model and joint model	- For stage 1 AKI, the median eGFR level was 73 ml/min/1.73 m^2 (IQR, 50-82) before admission and 78 ml/min/1.73 m^2 (IQR, 56-107) at discharge - For stage 2-3 AKI, the median eGFR level was 73 ml/min/1.73 m^2 (IQR, 51-87) before admission and 61 ml/min/1.73 m^2 (IQR, 37-96) at discharge - The short-term rate of eGFR decline was -12.3% (95% CI, -15.1 to -9.4 in patients with stage 1 AKI and -4.3% (95% CI, -7.0 to -1.4) in patients with stage 2-3 AKI - The long-term annual rate of eGFR decline was -1.5% (95% CI, -2.6 to -0.3) in patients with stage 1 AKI and -1.6% (95% CI, -2.7 to -0.5) in patients with stage 2-3 AKI
Nugent et al.,[116] JAMA Network Open, 2021	- Cohort study - USA - Five hospitals in Connecticut and Rhode Island - Electronic medical records and routinely collected laboratory results - 2020	- AKI patients tested for SARS-CoV-2 (*n* = 1,612) - Exposure: SARS-CoV-2 ($n_{SARS\text{-}CoV\text{-}2\ positive}$ = 182, $n_{SARS\text{-}CoV\text{-}2\ negative}$ = 1,430) - Outcome: eGFR level and rate of eGFR decline - Analysis: Linear mixed model and joint model	- Patients with SARS-CoV-2–associated AKI had a median eGFR level of 65.8 ml/min/1.73 m^2 (IQR, 46.3-85.9) at admission and 68.5 ml/min/1.73 m^2 (IQR, 48.2-93.8) at discharge. The mean rate of eGFR decline after AKI was -16.7 ml/min/1.73 m^2/year (95% CI, -43.4 to 10.0) - Patients with AKI not associated with SARS-CoV-2 had a median eGFR level of 63.9 ml/min/1.73 m^2 (IQR, 43.3-86.5) at admission and 58.4 ml/min/1.73 m^2 (IQR, 37.6-84.8) at discharge. The mean rate of eGFR decline after AKI was -2.7 ml/min/1.73 m^2/year (95% CI, –26.8 to 21.4)
Hsu et al.,[117] Clinical Kidney Journal, 2019	- Cohort study - USA - Kaiser Permanente Northern California - Research database including routinely and prospectively collected laboratory results - 2003-2008	- CKD patients (*n* = 444) - Exposure: AKI (*n* = 73*)* - Outcome: eGFR level and rate of eGFR decline - Analysis: Linear mixed model	- The rate of eGFR decline before AKI was -0.31 ml/min/1.73 m^2/year and the rate of eGFR decline after AKI was -0.98 ml/min/1.73 m^2/year - AKI increased the rate of eGFR decline by -0.67 ml/min/1.73 m^2/year (95% CI, -0.88 to -0.46) - When using both clinical and research sCr tests, AKI was associated with an increase in mean outpatient eGFR level of 2.01 ml/min/1.73 m^2 (95% CI, 1.17-2.84) - When using only research sCr tests, AKI was associated with a drop in mean outpatient eGFR level of -0.35 ml/min/1.73 m^2 (95% CI, -2.10 to 1.40)
Asar et al.,[118] Biometrical Journal, 2016	- Cohort study - UK - Salford Royal NHS Foundation Trust - Electronic medical records and routinely collected laboratory results - 2000-2013	- CKD patients (*n* = 2,289) - Exposure: AKI (*n* = 713) - Outcomes: Rate of eGFR decline - Analysis: Linear mixed model	- Before AKI, the annual decline in eGFR was 3.6% - After AKI, the annual decline in eGFR increased to 9.0% and 8.0% for AKI stage 1 and stage 2-3, respectively

D'hoore et al.,[119] Journal of Nephrology, 2015	- Cohort study - Belgium - Ghent University Hospital - Electronic medical records and routinely collected laboratory results - 2001-2013	- CKD patients (*n* = 311) - Exposure: AKI (*n* = 94) - Outcomes: eGFR level and rate of eGFR decline - Analysis: Absolute and percentage changes in eGFR	- The eGFR level decreased with 11 ml/min/1.73 m^2 (IQR, 0-22) from before to after AKI - The median rate of decline in eGFR before AKI was 5 ml/min/1.73 m^2/2.5 years (IQR, 0-13), and the median rate of decline in eGFR after AKI was 1 ml/min/1.73 m^2/2.5 years (IQR, 2-6)
James et al.,[120] Kidney International, 2010	- Cohort study - Canada - Alberta providence - Research database including routinely collected laboratory results - 2004-2006	- Patients undergoing coronary angiography with an eGFR <90 ml/min/1.73 m^2 (*n* = 10,418) - Exposure: AKI (*n* = 853) - Outcomes: Risk of decline in eGFR level and rate of eGFR decline - Analysis: Linear mixed model	- AKI was associated with a higher risk of a sustained decline in eGFR level three months after coronary angiography (no-AKI 5.6%; stage 1 AKI 28.2%; stage 2-3 AKI 59.1%) - The rate of eGFR decline was similar before and after coronary angiography for patients without AKI or with stage 1 AKI. Patients with stage 2-3 AKI had an increase in the rate of eGFR decline of 1.8 ml/min/1.73 m^2/year (95% CI, 0.6-3.0) after AKI
Amdur et al.,[121] Kidney International, 2009	- Cohort study - USA - Department of Veterans Affairs - Veterans Affairs Decision Support System database - 1999-2005	- ARF patients without CKD (*n* = 5,058) and with CKD (*n* = 44,377) - Exposure: Calendar time relative to the time of AKI - Outcome: eGFR level - Analysis: Estimation and comparison of mean eGFR for specified periods relative to the time of AKI (31-90, 91-365, and >365 days)	- In patients without CKD, ARF was associated with a relative drop in eGFR level of ~10% - In patients with CKD, ARF was not associated with changes in eGFR level
MEDLINE search query: (("Acute Kidney Injury"[Mesh]) OR ("Acute Kidney Injury"[tiab])) AND (("change in kidney function"[tiab]) OR ("decline in kidney function"[tiab]) OR ("kidney function decline"[tiab]) OR ("change in eGFR"[tiab]) OR ("decline in eGFR"[tiab]) OR ("eGFR decline"[tiab])) Hits: 244 Last updated: 14 February 2023			

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCr, serum creatinine.

2.6.3 Regional variation in incidence and prognosis of acute kidney injury (Study III)

Reported incidence rates of AKI vary considerably across countries.[27,122] However, only a few studies have examined domestic variation in AKI incidence (Table 4).[123-129] These studies cover countries in Asia, North America, South America, and Europe. Two studies from China used data from a nationwide cross-sectional survey and found only discrete regional variation in rates of AKI overall and community-acquired AKI among hospitalized patients, respectively.[126,128] In contrast, studies on KRT-requiring AKI from the USA[129] and the UK[127] reported substantial variation in incidences across geographical regions. Likewise, substantial regional variation in rates of AKI defined by diagnosis codes was reported in a study from Peru.[123] Of note, two recent UK studies showed conflicting results as one found substantial variation in AKI incidence rates across six counties of Ireland[124] while the other reported similar rates across three UK regions.[125]

As for the incidence of AKI, substantial country-to-country variation in CKD and mortality after AKI has been reported.[27] Furthermore, studies report domestic variation in mortality after AKI.[123,126-129] The aforementioned study from Peru reported regional age-standardized AKI-attributed mortality rates ranging from 0.4 to 10.1 per 100,000 people in the general population.[123] Moreover, a study from China reported an almost twofold difference in hospital mortality among AKI patients.[126] Although less prominent, studies from the UK and the USA have also reported variation in mortality after AKI.[127,129]

While previous studies provide insights into regional variation in AKI incidence and prognosis, most had methodological limitations. Studies based on diagnosis codes of AKI,[123] which are known to have a low sensitivity,[83-86] are at risk of bias due to regional differences in registration practices. Similarly, variation in regional treatment practices and availability of healthcare services could cause bias in studies restricting to patients with prior sCr tests,[124] hospitalized patients,[126,128] or KRT-requiring AKI.[127,129]

Table 4. Summary of the existing literature for Study III.

Study III: Regional variation in incidence and prognosis of acute kidney injury			
Author, journal, year	**Design, setting, data sources, period**	**Study population, AKI definition, exposure, outcome**	**Results**
Herrera-Añazco et al.,[123] Brazilian Journal of Nephrology, 2020	- Ecological study - Peru - National records provided by the Ministry of Health of Peru and census statics - 2005-2016	- Combination of patients with and without health insurance (~60% of the Peruvian population) - AKI defined by ICD-10 codes - Exposure: Region - Outcome: AKI and AKI-attributed mortality - Analysis: Standardization	- Age-standardized AKI rates across regions in 2011-2016 ranged from 4.3 to 28.0 per 100,000 person-years - Age-standardized AKI attributed mortality rates in 2011-2016 ranged from 0.4 to 10.1 per 100,000 person-years
Stack et al.,[124] Nephrology Dialysis Transplantation, 2018	- Cohort study - Ireland - The Northwest and Midwest regions - National Kidney Disease Surveillance System - 2005-2014	- Patients with a recorded sCr test (*n* = 451,646) - AKI defined by sCr - Exposure: Region - Outcome: AKI - Analysis: Standardization, logistic regression	- Crude AKI incidence rates across counties in 2014 ranged from 7.3 to 18.2 per 100 person-years - Differences in AKI incidence rates were not explained by differences in age, sex, baseline eGFR, location, laboratory measures of illness, or calendar year
Sawhney et al.,[125] BMJ Open, 2018	- Cohort study - UK - Grampian, Swansea, and Salford regions - EHR data - 2003, 2007, 2012	- Residents (*n* = 2,387,525) - AKI defined by sCr - Exposure: Region - Outcome: AKI - Analysis: Standardization	- Crude AKI incidence rates across regions ranged from 12.4 to 15.1 per 1,000 person-years - Age-and-sex-standardized AKI rates across regions ranged from 14.2 to 15.1 per 1,000 person-years
Wang et al.,[126] American Journal of Kidney Diseases, 2017	- Cross-sectional - China - 22 of 31 provinces (82% of the total population) - Laboratory data, medical records - 2013	- Hospitalized patients (*n* = 2,223,230) - AKI defined by sCr - Exposure: Province, tertile of northern latitude - Outcome: Community-acquired AKI among hospitalized patients and mortality among patients with community-acquired AKI - Analysis: Logistic regression	- The proportion of patients with community-acquired AKI varied from 0.95% to 1.13% across tertiles of northern latitude - Substantial differences in causes of AKI were found across tertiles of northern latitude - In-hospital mortality among patients with AKI ranged from 6.7% to 11.2% across tertiles of northern latitude

Kolhe et al.,[127] PLOS ONE, 2016	- Cohort study - UK - Nine regions in England - Hospital Episode Statistics from the National Health Service and census statics from the Office of National Statistic - 2000-2015	- Hospitalized patients (*n* = 203,758,879) - KRT-requiring AKI identified by combining ICD-10 codes for ARF with procedure codes for dialysis - Exposure: Region - Outcome: KRT-requiring AKI among hospitalized patients and mortality among patients with KRT-requiring AKI - Analysis: Logistic regression	- Rates of KRT-requiring AKI across regions ranged from 157.8 to 119.5 per 1,000,000 people in 2014-2015 - Mortality among patients with KRT-requiring AKI ranged from 23.7% to 37.8% across regions in 2000–2001 (estimates from 2014-2015 were not reported) - Differences in mortality persisted after adjusting for gender, age group, period of admission, AKI in diagnoses codes, admission method, CCI score, and ethnicity
Yang et al.,[128] Lancet, 2015	- Cross-sectional - China - 22 of 31 provinces (82% of the total population) - Laboratory data, medical records - 2013	- Hospitalized patients (*n* = 2,223,230) - Patients were screened for AKI based on changes in sCr. The diagnosis of AKI was confirmed using medical records - Exposure: Province - Outcome: AKI among hospitalized patients and in-hospital mortality among patients with AKI	- AKI occurred in 0.8-1.2% of hospitalized patients across regions - The highest incidence of AKI was found in the Southwest Region and the lowest in the North Region - In-hospital mortality among patients with AKI across regions ranged from 10.9% to 14.3%
Hsu et al.,[129] Clinical Journal of the American Society of Nephrology, 2013	- Cohort study - USA - Four US census-designated regions - The Nationwide Inpatient Sample and the US Census Bureau - 2007-2009	- Hospitalized patients (*n* = 448,755) - KRT-requiring AKI identified by combining ICD-10 codes for ARF with procedure codes for dialysis - Exposure: Region - Outcomes: KRT-requiring AKI among hospitalized patients and in-hospital mortality among patients with KRT-requiring AKI - Analysis: Poisson regression	- Crude incidence rates of KRT-requiring AKI across regions ranged from 459 to 524 cases per 1,000,000 person-years - Regional differences persisted after adjustment for differences in sex and age - In-hospital mortality associated with KRT-requiring AKI ranged from 19.4% to 25.9%
MEDLINE search query: ("Acute Kidney Injury"[Mesh] OR "Acute Kidney Injury"[tiab]) AND ("Inciden*"[tiab] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR "Prevalen*"[tiab]) AND ((“geogra*”[tiab]) OR (“regio*”[tiab])) Hits: 352 Last updated: 14 February 2023			

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD, International Classification of Disease; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, kidney replacement therapy; sCr, serum creatinine.

2.6.4 Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease (Study IV)

AKI has consistently been associated with increased risks of CKD,[48,49,55,130] CVD,[45,50-53,130,131] and death.[45,132,133] Furthermore, the duration of AKI has associated with mortality.[134-136] Similarly, the associations between AKI duration and CKD and CVD have been studied[54,114,115,137-149] (Table 5) and reviewed.[52,134,135]

Studies examining the association between AKI duration and CKD generally point towards higher risks of CKD with increasing duration of AKI.[114,115,137,138,140-146,148] Similarly, two systematic reviews reported higher risks of CKD with increasing AKI duration, although the reviews only included two studies each and were limited by varying definitions of AKI duration.[134,135] The association between AKI duration and CKD is most apparent in studies comparing non-recovery with recovery beyond the first days of AKI, e.g., at discharge or 90 days after AKI onset.[114,115,146,148] When examining the importance of AKI duration in the phase immediately following AKI onset, findings indicate an increased risk of CKD if AKI persists for more than two to three days.[137,140,142,144,145] Nonetheless, results lack consistency and other studies did not find an association between AKI duration and CKD.[139,149] Importantly, no studies have examined the impact of AKI duration on the long-term risk of CKD in a population-based setting using the ADQI consensus definition of AKI duration.[80]

Studies examining the association between AKI duration and CVD are few and have shown inconsistent results.[54,139,147,148] AKI duration has been associated with rates of heart failure, but results vary and lack precision.[54,139,147,148] This corresponds to findings pertaining to other cardiovascular outcomes, such as stroke and myocardial infarction.[147,148] The disparity of findings is reflected by two systematic reviews, which assessed the association between AKI duration and heart failure.[52,134] The reviews arrived at divergent conclusions as one reported a higher risk of heart failure with increasing AKI duration, while the other did not.[52,134]

Collectively, the studies examining the association between AKI duration and CVD or CKD used narrowly defined study populations,[54,115,137,139,140,142-144,146-149] small cohorts (<1000 AKI cases),[54,115,137,139,140,142-144,149] and non-consensus definitions of AKI or AKI duration.[54,115,140-143,145,146,148,149] In addition, most studies only considered outcomes within a few years of follow-up.[137,138,142-147]

Table 5. Summary of the existing literature for Study IV.

Study IV: Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease			
Author, journal, year	**Design, setting, data sources, period**	**Study population, exposure, outcome, analysis**	**Results**
Ozrazgat-Baslanti et al.,[137] Annals of Surgery, 2022	- Cohort study - USA - UF Health Shands Hospital, Florida - 2015-2017	- Critically ill surgical sepsis patients (*n* = 239) - Exposure: AKI duration defined as rapidly reversed (<48 hrs.) and persistent (≥48 hrs.) with the latter subdivided according to recovery status at discharge - Outcome: MAKE defined as a composite of death, dependency on KRT, or decrease in eGFR to <60 ml/min/1.72 m^2 - Analysis: Unadjusted proportions	- MAKE at 1 year after AKI occurred in 29% of patients with rapidly reversed AKI, 43% of patients with persistent AKI with recovery at discharge, and 55% of patients with persistent AKI without recovery at discharge
Wang et al.,[138] BMC Medicine, 2022	- Cohort study - UK - Regions of Tayside and Fife - Health Informatics Centre at the University of Dundee - 2010-2018	- Adult residents with AKI and recovery within 90 days (*n* = 56,906) - Exposure: Recovery defined as early or delayed based on status at day seven after AKI onset - Outcome: CKD - Analysis: Cox proportional hazards regression	- The 1-year HR for CKD was 2.21 (95% CI, 1.91-2.57) for delayed recovery compared with early recovery
Haines et al.,[115] Scientific Reports, 2021	- Cohort study - UK - Single center - Electronic medical records, routinely collected laboratory results, and national registries - 2004-2008	- ICU patients with AKI (*n* = 1,509) - Exposure: Recovery status at discharge - Outcome: Composite of chronic dialysis and death - Analysis: Cox proportional hazards regression	- Among all AKI patients, non-recovery was associated with a HR of 1.30 (95% CI, 1.06-1.60) for death or chronic dialysis when compared with recovery - Among AKI patients with available eGFR data during follow-up, non-recovery was associated with a HR of 1.11 (95% CI 0.76–1.61) for death or chronic dialysis when compared with recovery
Ikizler et al.,[139] Kidney International, 2020	- Cohort study - USA and Canada - Four North American clinical centers - 2009-2018	- AKI patients (*n* = 769) and matched non-AKI patients (*n* = 769) - Exposure: AKI and AKI duration (≤1, 2-3, 4-6, ≥7 days) - Outcome: CKD, CKD progression, heart failure - Analysis: Fine-Gray subdistribution hazards regression	- Mean follow-up was 4.5 years - AKI was associated with higher rates of CKD, CKD progression, and heart failure than no AKI - No clear association between AKI duration and rates of CKD and CKD progression - For heart failure there was a trend of higher rates with increasing duration of AKI although results lacked precision

Bhatraju2020 et al.,[140] JAMA Network Open, 2020	- Cohort study - USA and Canada - Four North American clinical centers - 2009-2018	- AKI patients (*n* = 769) and matched non-AKI patients (*n* = 769) - Exposure: AKI and AKI duration (defined as resolving if ≤3 days and otherwise defined as non-resolving) - Outcome: MAKE defined as incident or progressive CKD, long-term dialysis, or all-cause death - Analysis: Cox proportional hazards regression	- Mean follow-up was 4.7 years - Among all AKI patients, 475 (62%) had resolving AKI and 294 (38%) had non-resolving AKI - Non-resolving AKI was associated with a HR of 1.51 (95% CI, 1.22-1.88) for MAKE compared with resolving AKI. The association was mainly due to increased rates of CKD [HR 2.40 (95% CI, 1.65-3.49)]
Siew et al.,[141] American Journal of Kidney Diseases, 2020	- Cohort study - USA - Department of Veterans Affairs - 2002-2014	- Hospitalized patients with stage 2-3 AKI and recovery within 90 days (*n* = 47,903) - Exposure: Time to recovery divided into four intervals: 1-4, 5-10, 11-30, and 31-90 days - Outcome: Composite of a ≥40% sustained decline in eGFR or kidney failure - Analysis: Cox proportional hazards regression	- Median follow-up was 3.5 years - 29,316 (61%) recovered by 1-4 days, 10,360 (22%) by 5-10 days, 4,520 (9%) by 11-30 days, and 3,707 (8%) by 31-90 days - Compared with patients with recovery within 1-4 days, HRs for the composite outcome were 1.33 (95% CI, 1.24-1.43), 1.41 (95% CI, 1.28-1.54), and 1.58 (95% CI, 1.43-1.75) for patients with recovery during the 5-10, 11-30, or 31-90 day periods, respectively
Bravi et al.,[142] European Urology, 2019	- Cohort study - USA - Memorial Sloan Kettering Cancer Center, New York - 1989-2018	- Partial nephrectomy patients (*n* = 1,977) (388 patients with AKI) - Exposure: AKI and AKI duration (1, 2-3, ≥4 days) - Outcome: Recovery to ≥90% of baseline eGFR - Analysis: Unspecified regression models	- Compared with no AKI, the probability of ≥90% recovery of baseline eGFR within 1 year after surgery was 0.40, 0.30, and 0.08 for an AKI duration of 1, 2-3, and ≥4 days, respectively.
Mizota et al.,[143] Journal of Critical Care, 2019	- Cohort study - Japan - Kyoto University Hospital - 2008-2015	- Abdominal surgery patients (*n* = 3,751) (258 patients with AKI) - Exposure: AKI duration defined as transient (≤7 days) and persistent (>7 days) - Outcome: CKD progression - Analysis: Cox proportional hazards regression	- 216 (84%) of AKIs were transient and 42 (16%) were persistent - Compared with patients without AKI, the ORs of CKD progression at 1 year after surgery were 2.01 (95% CI, 1.34–2.93) for transient AKI and 6.20 (95% CI, 3.00–11.43) for persistent AKI
Palomba et al.,[144] Journal of Nephrology, 2017	- Cohort study - Brazil - The Heart Institute, University of São Paulo - 2003-5, 2006-7	- Elective cardiac surgery patients without CKD (*n* = 215) (43 patients with AKI) - Exposure: Duration of AKI in days - Outcome: CKD stage ≥3 - Analysis: Multiple logistic regression	- AKI duration >3 days was associated with an OR of 13.48 (95% CI 4.15-43.7) for CKD within 1 year after surgery compared with no AKI

Heung et al.,[145] American Journal of Kidney Diseases, 2016	- Cohort study - USA - Department of Veterans Affairs - 2011	- Hospitalized patients with a baseline eGFR >60 ml/min/1.72m^2 (*n* = 104,764) (17,049 patients with AKI) - Exposure: AKI duration defined as fast (≤2 days), intermediate (3-10 days), slow or no recovery (>10 days), and unknown (no sCr test within 10 days following AKI onset) - Outcome: CKD stage ≥3 - Analysis: Modified Poisson regression	- For stage 1 AKI, the adjusted 1-year RRs for CKD were 1.43 (95% CI, 1.39-1.48), 2.00 (95% CI, 1.88-2.12), 2.65 (95% CI, 2.51-2.80), and 1.48 (95% CI, 1.14-1.64) for fast, intermediate, slow or no recovery, and unknown recovery, respectively, when compared with patients without AKI - Similar patterns were observed for stage 2 and stage 3 AKI
Pannu et al.,[146] Clinical Journal of the American Society of Nephrology, 2013	- Cohort study - Canada - Alberta Health and Wellness, the Northern and Southern Alberta Renal Programs, and the provincial laboratories of Alberta - 2002-2007	- Hospitalized AKI patients (*n* = 3,231) - Exposure: AKI duration >/≤90 days - Outcomes: Adverse renal outcome (sustained doubling of sCr or kidney failure) - Analysis: Cox proportional hazards regression	- Median follow-up was 2.8 years - 2247 (65.5%) had an AKI duration ≤90 days - AKI duration o>90 days was associated with a HR of 4.13 (95% CI, 3.38-5.04) for adverse renal outcomes when compared with AKI duration ≤90 days
Gammelager et al.,[147] Critical Care, 2014	- Cohort study - Denmark - The North and Central Denmark regions - Population-based medical databases - 2005-2010	- ICU patients (*n* = 21,556) (4,792 patients with AKI) - Exposure: AKI and recovery status at the time of discharge - Outcomes: Heart failure, myocardial infarction, and stroke - Analysis: Cox proportional hazards regression	- 3,888 (81%) of AKI patients recovered kidney function by the time of discharge - The HRs for heart failure were 1.26 (95% CI, 1.00-1.60) for stage 1 AKI with recovery and 1.81 (95% CI, 1.07-3.07) for stage 1 AKI without recovery when compared with patients without AKI. Results were similar for stage 2-3 AKI - The HRs for myocardial infarction were 1.05 (95% CI, 0.72-1.55) for stage 1 AKI with recovery and 0.79 (95% CI, 0.25-2.51) for stage 1 AKI without recovery when compared with patients without AKI. For stage 2-3 AKI, the HRs were 1.31 (95% CI, 0.83-2.07) for AKI with recovery and 1.97 (95% CI, 1.17-3.32) for AKI without recovery when compared with patients without AKI - AKI with or without recovery was not associated with higher rates of stroke when compared with patients without AKI

Wu et al.,[114] Kidney International, 2011	- Cohort study
	- Taiwan
	- National Taiwan
	- University Hospital Study Group on Acute Renal Failure
	- 2002-2008
		- Patients admitted to an ICU after major surgery (*n* = 9,233)
		- Exposure: AKI and recovery status at discharge
		- Outcome: Long-term dialysis
		- Analysis: Cox proportional hazards regression
			- Median follow-up was 4.6 years
			- Compared with non-CKD patients without AKI, the HRs for long-term dialysis were:
			  - 212.7 (95% CI, 105.5-428.8) for CKD patients without recovery
			  - 74.1 (95% CI, 38.8-141.3) for CKD patients with recovery
			  - 61.0 (95% CI, 24.1-154.0) for non-CKD patients without recovery
			  - 42.6 (95% CI, 20.8-87.3) for CKD patients without AKI
			  - 4.5 (95% CI, 2.4-8.4) for non-CKD patients with recovery

Choi et al.,[148] Kidney International, 2010	- Cohort study
	- USA
	- Department of Veterans Affairs
	- 1986-2006
		- Hospitalized HIV-infected patients (*n* = 17,325) (3,060 patients had AKI)
		- Exposure: AKI and recovery at discharge
		- Outcomes: Heart failure, CVD (including coronary, cerebrovascular, or peripheral arterial disease), and kidney failure with replacement therapy
		- Analysis: Cox proportional hazards regression
			- Mean follow-up was 5.7 years
			- Compared with no AKI:
			  - The HRs for heart failure were:
			  - 1.00 (95% CI, 0.63-1.59) for stage 1 AKI with recovery
			  - 1.45 (95% CI, 0.90-2.34) for stage 1 AKI without recovery
			  - 1.90 (95% CI, 0.76-4.71) for stage 2-3 AKI with recovery
			  - 2.38 (95% CI, 0.88-6.42) for stage 2-3 AKI without recovery
			  - The HRs for CVD were:
			  - 1.01 (95% CI, 0.76-1.35) for stage 1 AKI with recovery
			  - 0.93 (95% CI, 0.64-1.34) for stage 1 AKI without recovery
			  - 1.22 (95% CI, 0.62-2.41) for stage 2-3 AKI with recovery
			  - 1.67 (95% CI, 0.65-4.29) for stage 2-3 AKI without recovery
			  - The HRs for kidney failure with replacement therapy were:
			  - 0.89 (95% CI, 0.58-1.35) for stage 1 AKI with recovery
			  - 2.18 (95% CI, 1.52-3.13) for stage 1 AKI without recovery
			  - 2.51 (95% CI, 1.34-4.70) for stage 2-3 AKI with recovery
			  - 10.62 (95% CI, 4.99-22.60) for stage 2-3 AKI without recovery

van Kuijk et al.,[149] Clinical Journal of the American Society of Nephrology, 2010	- Cohort study - Netherlands - Department of Vascular Surgery, Erasmus Medical Center - 1990-2008	- Patients undergoing elective major vascular surgery (*n* = 1,308) - Exposure: Changes in eGFR on day 1-3 after surgery defined as no change (within 10% of baseline), temporary decline (a decline >10% followed by complete recovery to within 10% by day 3), and persistent decline (a decline >10 % was present on day 3) - Outcome: CKD - Analysis: multivariate logistic regression	- Median follow-up was 5 years - Temporary decline was associated with a RR of 3.4 (95% CI, 2.7-4.1) and persistent decline with a RR of 3.6 (95% CI, 2.8-4.4) for CKD when compared with no change

Goldberg et al.,[54] Kidney International, 2009	- Cohort study
	- Israel
	- Rambam Medical Center, Haifa
	- 2000-2007
		- Patients with myocardial infarction (*n* = 1,957)
		- Exposure: AKI severity and recovery status at discharge (transient/persistent)
		- Outcome: Heart failure and recurrent myocardial infarction
		- Analysis: Cox proportional hazard model
			- Median follow-up was 3 years
			- Mild and moderate/severe AKI occurred in 156(8%) and 138(7%) of patients, respectively
			- Mild AKI was transient in 61 (39%) and moderate/severe AKI was transient in 60 (44%) patients
			- When compared with patients without AKI:
			  - The HRs of heart failure were:
			  - 1.5 (95% CI, 0.8-2.8) for transient, mild AKI
			  - 1.7 (95% CI, 1.1-2.8) for persistent, mild AKI
			  - 1.7 (95% CI, 1.1-2.9) for transient, moderate/severe AKI
			  - 2.0 (95% CI, 1.2-3.3) for persistent, moderate/severe AKI
			  - The HRs of recurrent infarction were:
			  - 0.6 (95% CI, 0.2-1.8) for transient, mild AKI
			  - 1.6 (95% CI, 0.9-1.8) for persistent, mild AKI
			  - 1.4 (95% CI, 0.7-3.0) for transient, moderate/severe AKI
			  - 1.4 (95% CI, 0.7-2.8) for persistent, moderate/severe AKI

MEDLINE search query: (("Acute Kidney Injury"[Mesh] OR "Acute Kidney Injury"[tiab]) AND (("Cardiovascular Diseases"[Mesh]) OR ("Renal Insufficiency"[Mesh]) OR ("Glomerular Filtration Rate"[Mesh])) AND ("recover*"[tiab]) AND (("Time"[MesH]) OR ("timin*"[tiab]) OR ("patter*" [tiab]) OR ("degre*" [tiab]) OR ("duratio*"[tiab])) AND (humans[mh]))
Hits: 851
Last updated: 14 February 2023

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; KRT, kidney replacement therapy; MACE, major atherosclerotic cardiovascular event; MAKE, major adverse kidney event; OR, odds ratio; RR, relative risk; sCr, serum creatinine.

2.7 Knowledge gaps

2.7.1 Routine clinical care creatinine data in Denmark (Study I)

In Denmark, laboratory data have been collected in the Clinical Laboratory Information System Research Database (LABKA) from the North Denmark Region and the Central Denmark Region since the 1990s and nationwide in the Register of Laboratory Results for Research (RLRR) since 2013.[150,151] Although LABKA and the RLRR have been reviewed with regard to structure and content, the detailed geographical coverage of the databases and the characteristics of patients with pCr tests have not been examined. Combined, these databases could offer both nationwide and long-term coverage of pCr data, which holds the potential of being a valuable source of information for studies on kidney disease epidemiology. Thus, a detailed description of the available population-based pCr data from these databases is warranted.

2.7.2 Kidney function before and after acute kidney injury (Study II)

Findings from studies examining the association between AKI and changes in kidney function are inconsistent and most studies are limited methodologically or by focusing on specific patient populations. Specifically, there is a scarcity of studies among patients with a baseline eGFR ≥60 ml/min/1.73 m^2. Furthermore, no studies have examined the association between AKI and changes in kidney function in a population-based cohort defining AKI by the KDIGO creatinine criteria. Information on changes in eGFR level and eGFR slope from before to after AKI in a general population cohort is central for understanding the mechanisms linking acute and chronic kidney diseases and for optimizing follow-up in patients with AKI.

2.7.3 Regional variation in AKI incidence and prognosis (Study III)

Studies conducted in different countries and healthcare settings have reported domestic variation in AKI incidence and mortality after AKI. Moreover, even studies from geographically small countries with public healthcare have reported regional variation in AKI incidence and mortality after AKI. However, no studies have examined regional variation in clinical and biochemical follow-up and the incidence of CKD following AKI. Knowledge about variations in the incidence, clinical care, and outcomes of AKI in a universal healthcare system may reveal unwarranted inequalities in healthcare, which could aid in optimizing clinical care and guide the allocation of resources.

2.7.4 Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease (Study IV)

Although studies have been conducted in this field, the associations between AKI duration and CKD and CVD remain unclear. Most studies have examined selected study populations and not used current consensus definitions of AKI or AKI duration, which hampers the comparison and transportability of the results. No studies have examined the long-term impact of AKI duration on the risks of CKD and CVD in a population-based setting using the ADQI consensus definition of AKI duration.

Knowledge about differences in risks of CKD and CVD based on AKI duration could help inform both patients with AKI and physicians about the prognosis following AKI and assist in the planning of nephrology follow-up. Additionally, information about the impact of AKI duration on CKD and CVD development could identify a potential target for AKI-directed treatments. Therefore, a population-based study on the significance of AKI duration for the development of CKD and CVD using consensus definitions for AKI and AKI duration is warranted.

3. Hypotheses and aims

The overall aim of this PhD dissertation was to expand the current knowledge on the occurrence and prognosis of AKI through the following four studies:

3.1 Routine clinical care creatinine data in Denmark (Study I)

Hypothesis: The timepoint of complete geographical coverage of pCr data in LABKA and the RLRR differs considerably on a regional and municipal level. Individuals with pCr tests are older and more comorbid than the general population. A large proportion of Danish residents are tested each year.

Aim: To explore the availability of pCr data in LABKA and the RLRR. More specifically, to identify the timepoint when municipalities and regions were covered by the databases, to describe characteristics of the pCr-tested cohort and the general population, and to assess the annual proportion of Danish residents with a pCr test.

3.2 Kidney function before and after acute kidney injury (Study II)

Hypothesis: AKI is associated with an unrecovered drop in eGFR level and an accelerated rate of eGFR decline (i.e., a steeper eGFR slope after AKI compared with before AKI).

Aim: To examine the associations between AKI and changes in eGFR level and eGFR slope and to explore whether these associations vary according to patient characteristics, including baseline eGFR level.

3.3 Regional variation in incidence and prognosis of acute kidney injury (Study III)

Hypothesis: AKI incidence and CKD, mortality, and follow-up after AKI vary across the five Danish regions.

Aim: To examine the incidence of AKI across the Danish regions and compare rates of CKD, mortality, and follow-up after AKI accounting for differences in patient characteristics.

3.4 Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease (Study IV)

Hypothesis: The duration of AKI is a risk factor for CKD and CVD.

Aim: To examine cumulative incidences of CKD and CVD according to AKI duration. To explore the impact of AKI duration on the rates of CKD and CVD accounting for differences in patient characteristics.

4. Methods

The following section describes the materials and methods used in Studies I-IV and includes an overview presented in Table 6.

4.1 Setting

The four studies included in this dissertation were conducted in Denmark, which had 5.8 million residents in 2018.[152] Denmark has a universal healthcare system allowing for tax-funded access to healthcare services, including general practitioners and specialized care.[153] The majority of specialized care, including care for patients with kidney diseases, is being offered by public hospitals.[153] Furthermore, public hospital-based laboratories collect and analyze blood samples drawn in general practices, at hospitals, and in other specialized care facilities in Denmark and test results are recorded in central databases.[150,151]

The administration of the Danish healthcare system is divided into three levels.[153] On the national level, healthcare legislation, planning, and financing are regulated by the government through the Ministry of Health. On the regional level, the five Regions (the Central Denmark Region, the North Denmark Region, the Region of Southern Denmark, Region Zealand, and the Capital Region of Denmark) are the main administrative units of primary and secondary healthcare services, including hospitals, general practices, and private practices specialists. Finally, on the local level, the 98 municipalities administer and oversee services such as home care and rehabilitation.[153]

4.2 Data sources

Denmark has a long tradition of collecting and storing healthcare data in population-based medical databases.[153,154] These databases are renowned for their high quality and represent a unique resource for register-based research. Exact individual-level linkage across medical databases is achieved by the use of the civil registration number, which is a unique 10-digit personal identifier assigned to all Danish residents at birth or upon immigration.[155]

All studies in this dissertation used data from the Danish registries. The following section will give a brief introduction to the included registries.

The Danish Civil Registration System (CRS)[155] was established in 1968. In addition to the civil registration number, the register records individual-level information such as sex, date of birth, address, civil status,

vital status, and migration. From this register, we used information on sex and age (Studies I-IV), address (Studies I and III), civil status (Study III), and vital status (Studies II-IV).

The Clinical Laboratory Information System Research Database (LABKA)[150] records laboratory information on biomarkers, including blood samples drawn in general practices, outpatient clinics, emergency rooms, or at hospitals, analyzed at hospital-based laboratories in the North Denmark Region and the Central Denmark Region. Besides test results, the database contains information such as civil registration number, date and time of sampling, and unit of measurement. Recordings to the database started in the 1990s.[150] The assay used for measuring pCr changed from Jaffe´s method to enzymatic methods during 2004–2008 and standardization to an isotope mass spectrometry reference was implemented during 2004-2010.[24] From this database, we used information on pCr tests (Studies I, II, and IV).

The Register of Laboratory Results for Research (RLRR)[151] records nationwide laboratory information on biomarkers covering the same clinical settings as LABKA. In addition to test results, the database contains information such as civil registration number, date and time of sampling, and unit of measurement. Reporting to the database started in 2013.[151] From this database, we used information on urine dipstick tests and measurements of pCr, urine albumin concentration, urine albumin excretion rate, and urine albumin-creatinine ratio (Studies II-IV).

The Danish National Patient Registry (DNPR)[154] contains information on admissions to non-psychiatric hospitals since 1977 and admissions to emergency clinics, outpatient clinics, and psychiatric hospitals since 1995. The registry holds information on dates of admission and discharge, examinations, diagnoses, and procedures performed (including KRT and surgical procedures). For each contact, the primary diagnosis and an optional number of secondary diagnoses are recorded according to the international classification of diseases (ICD) 8th revision until 1994 and ICD 10th revision thereafter. We used information from this registry to define various covariates (Studies I-IV) and outcomes (Studies III-IV).

The Danish National Prescription Registry (NPR)[156] holds individual-level information on all prescriptions for drugs dispensed in Danish pharmacies or used at nursing homes since 1995. The registry records information on the dispensing date, number and size of dispensed packages, and the Anatomical Therapeutic Chemical (ATC) code of the dispensed drug. We used information on prescription drug use as a covariate in all studies.

The National Health Service Registry (NHSR)[157] has been recording information on services provided by private practicing health professionals, including general practitioners and practicing medical specialists since 1990. The registry contains information on the type and specialty of the provider and the date and

type of services provided. From this registry, we used information on contact with a general practitioner (Study I) and urine dipstick tests (Study III).

The Danish National Pathology Registry[158] holds nationwide information on all pathology examinations, including kidney biopsies, performed in Denmark since 1997. In addition to information on diagnosis according to the Danish version of the Systemized Nomenclature of Medicine (SNOMED) codes, the registry contains information on the requesting department or general practitioner, procedures performed, and microscopy descriptions. From this registry, we used information on kidney biopsies (Study I).

Statistics Denmark[159] provides a publicly available resource entitled "StatBank Denmark" containing aggregated census information, including information on the number of residents in municipalities and regions by age and sex. From this register, we retrieved information on the general population (Studies I and III).

4.3 Study designs and populations

The four studies included in this dissertation are population-based cohort studies.

In Study I, individuals with one or more pCr tests recorded in LABKA or the RLRR from 1 January 1990 to 31 December 2018 were included. Additionally, we sampled a general population cohort using a 2% monthly random sample of Danish residents in 2016-2018.

For Studies II-IV, the study populations included patients with AKI. AKI was identified by implementing the KDIGO creatinine criteria using a three-step approach (Figure 2):

1) An absolute increase in pCr of ≥26.5 µmol/l within 48 hours *or*
2) a relative increase of ≥1.5 times the lowest pCr test within the last seven days *or*
3) a relative increase of ≥1.5 times the baseline pCr level, which was defined as the median outpatient pCr test within the previous 8-365 days. In this setting and throughout, we use the term "outpatient pCr" to cover pCr tests drawn outside the acute hospital setting meaning tests from primary care and planned outpatient visits.

Using this approach, each pCr test was evaluated by comparison with prior pCr tests and AKI was identified if one or more of the aforementioned criteria were fulfilled. Tests from patients with kidney failure were censored (kidney failure is defined in the Outcomes section below).

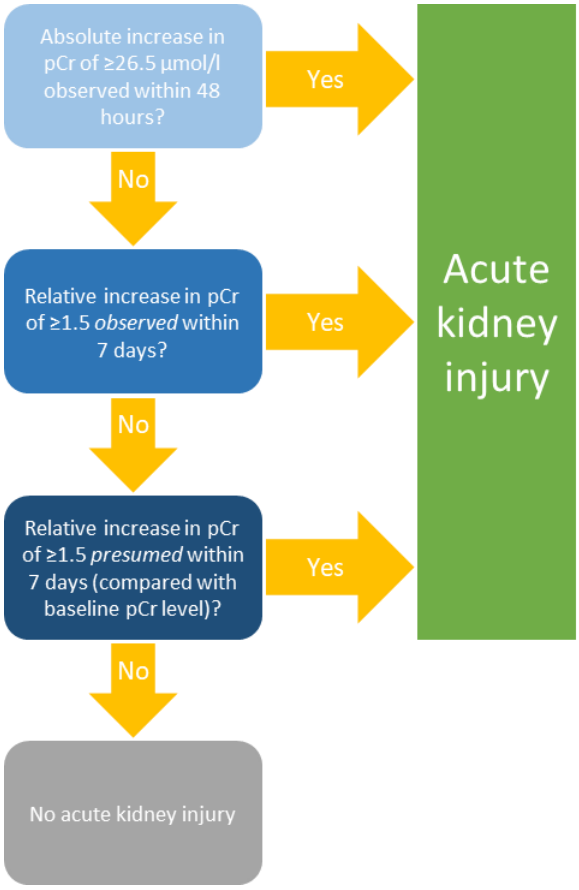

Figure 2. Implementation of the KDIGO creatinine criteria for acute kidney injury. Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes; pCr, plasma creatinine.

In Study II, adults (≥18 years of age) with a first-time laboratory-recorded AKI were identified in LABKA or the RLRR from 1 April 2010 to 31 December 2017. This period was chosen to ensure that pCr tests were analyzed using standardized isotope dilution mass spectrometry.[24] Included patients were required to have three or more outpatient pCr tests more than seven days before AKI and spanning at least 90 days, with one test drawn within 365 days before AKI, as well as three or more outpatient pCr tests spanning at least 90 days from day 91 after AKI and onwards.

In Study III, two study populations were used. The incidence of AKI was estimated using a study population that included all adults (≥18 years of age) in 2017. When examining CKD, mortality, and biochemical follow-up after AKI, the study population included patients with AKI in 2017. This study period was chosen to ensure one year of laboratory look-back and one year of follow-up for all regions.[160] To prevent including the same AKI episode more than once in estimates of AKI incidence, we defined the duration of an AKI episode as 90 days.

In Study IV, adults (≥18 years of age) with a first-time laboratory-recorded AKI in LABKA or the RLRR from 1 January 1990 to 31 December 2018 were identified. To ensure that AKIs were incident, only AKIs with onset

more than 90 days after the first recorded pCr test and with no pCr test fulfilling the AKI definition in that period were considered. To enable categorization of AKI duration, included patients were required to have an outpatient baseline pCr test 8-365 days before AKI and an assessment of AKI duration by one or more pCr tests within the first seven days after AKI onset. Patients without a baseline eGFR measurement and assessment of AKI duration within the first seven days were described but not included in the analyses.

4.4 Exposures

Study I was a descriptive study of the pCr data recorded in LABKA and the RLRR. When evaluating if municipalities and regions were covered by the laboratory databases the exposure was calendar month and year. When assessing the annual proportions of Danish residents with a recorded pCr test the exposure was calendar year. The characterization of pCr-tested individuals and the general population was purely descriptive and did not include an exposure.

Study II was a descriptive study of changes in eGFR from before to after AKI. Therefore, eGFR was modeled as a function of time before and after AKI.

In Study III, the exposure was the region of residence in 2017.

In Study IV, the exposure was AKI duration. In accordance with the ADQI definition, we categorized AKIs using three duration groups: 1) Rapid reversal AKI, if a pCr test <48 hours after AKI onset did not fulfill the AKI criteria and this reversal was followed by ≥48 hours without a new pCr test fulfilling the AKI criteria; 2) persistent AKI, if not fulfilling criterion 1) and a pCr test within two to seven days after AKI onset did not fulfill the AKI criteria and this was followed by ≥48 hours without a new pCr test fulfilling the AKI criteria; 3) AKD, if neither 1) nor 2) were fulfilled.[80]

4.5 Outcomes

4.5.1 Complete geographical coverage of the laboratory databases (Study I)

When assessing the coverage of the laboratory databases, the outcome was complete geographical coverage on a municipal and a regional level. The coverage of the laboratory databases was evaluated using a visual inspection of the number of recorded pCr tests from each municipality (Figure 3). The geographical coverage was considered complete when the daily numbers of reported pCr tests from each municipality reached a stable level.

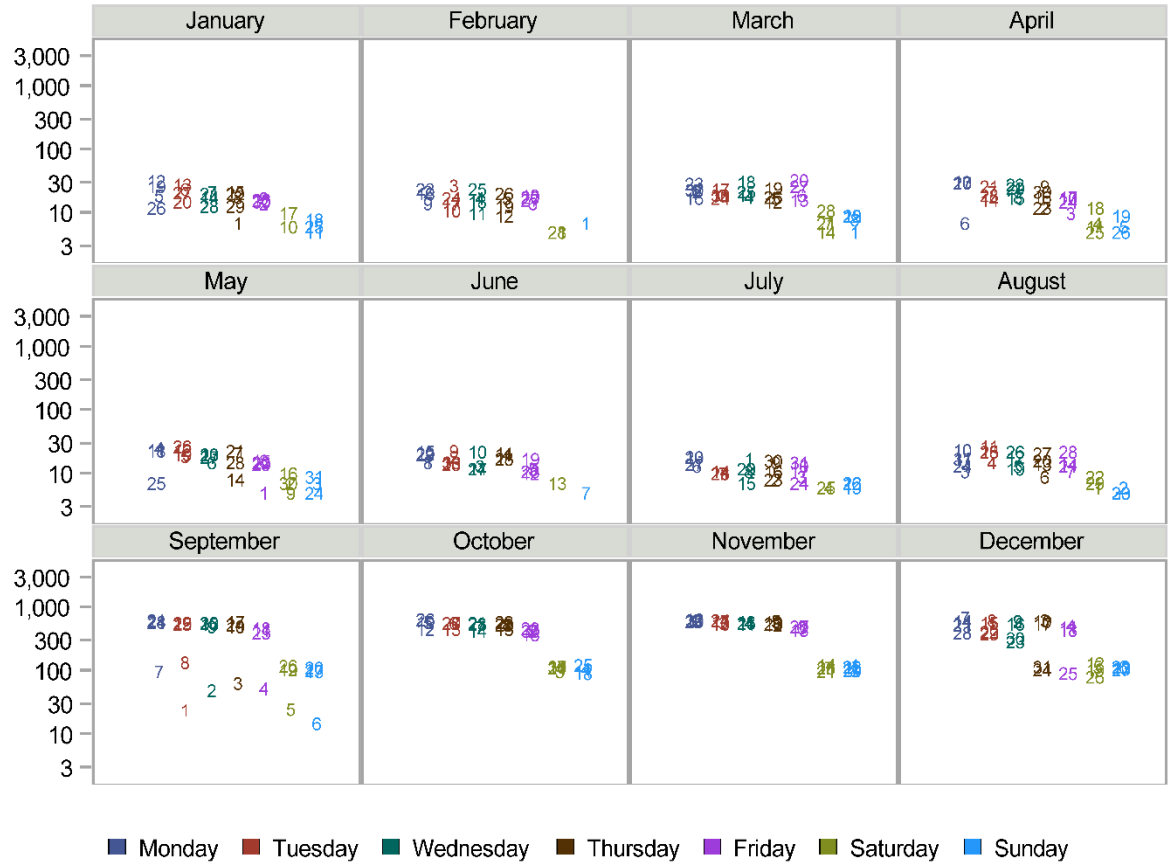

Figure 3. Typical pattern of reporting to the laboratory databases (municipality of Vejle in 2015). Notes: The numbers in each panel represent the date within the month and the color of the number indicates the day of the week. The position on the y-axis indicates the number of tests recorded on a given date. Here, we considered November to be the first month with complete reporting throughout. Note that due to the Christmas holidays, there is an expected drop in testing in late December. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Sørensen HT, Christiansen CF. Routine Clinical Care Creatinine Data in Denmark - An Epidemiological Resource for Nationwide Population-Based Studies of Kidney Disease. Clinical epidemiology. 2022;14:1415-1426. doi:10.2147/CLEP.S380840,* (Appendix I)[160].

4.5.2 Changes in eGFR level and eGFR slope (Study II)

In Study II, the outcome was eGFR as a function of time before and after AKI. Specifically, this covered eGFR levels and eGFR slopes before and after AKI and the difference in eGFR levels and slopes from before to after AKI. eGFR was estimated from pCr using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, assuming non-black race.[161]

4.5.3 Mortality (Studies II-IV)

All-cause mortality was an outcome in Study III (in addition to being used descriptively in Study II and as a competing event in Study IV). In all four studies, information on death was obtained using the CRS, which is considered virtually complete.[155]

4.5.3 Biochemical follow-up after acute kidney injury (Study III)

Biochemical follow-up after AKI included urine dipstick tests and measurements of pCr, urine albumin (including urine albumin concentration and urine albumin excretion rate), and urine albumin-creatinine ratio performed by general practitioners or specialists. Information on all tests was obtained from the RLRR.[151] Furthermore, information on dipstick tests performed by general practitioners was retrieved from the NHSR.[157] Biochemical follow-up was evaluated during the three months from the end of the AKI episode to not include tests performed during the AKI episode.

4.5.4 Outpatient contact with a nephrology department (Study III)

Outpatient contact with a nephrology department was defined by a recording of an outpatient hospital contact with a nephrology department in the DNPR and evaluated during the six months following AKI onset to cover both the AKI episode and the subsequent three months.

4.5.5 Chronic kidney disease (Studies III-IV) and kidney failure (Studies II-IV)

CKD and kidney failure were defined using a combination of pCr tests from LABKA and the RLRR and diagnosis and procedure codes from DNPR.[162]

The definition of CKD included: 1) The first observation of two or more outpatient eGFR measurements of <60 ml/min/1.73 m^2 separated by >90 days; 2) a hospital diagnosis of CKD stage 3-5, dependency of KRT, or kidney transplantation; or 3) a hospital procedural code of KRT due to CKD or kidney transplantation. Correspondingly, the definition of kidney failure included: 1) The first observation of two or more outpatient eGFR measurements of <15 ml/min/1.73 m^2 separated by >90 days; 2) a hospital diagnosis of CKD stage 5, dependency of KRT, or kidney transplantation; or 3) a hospital procedural code of KRT due to CKD or kidney transplantation. The time of CKD or KF was defined as the date of the first CKD-defining diagnosis or procedure code or the date of the second defining eGFR measurement more than 90 days after the first defining eGFR measurement.

4.5.6 Cardiovascular disease (Study IV)

In Study IV, the composite outcome of CVD included atrial fibrillation and flutter, ischemic heart disease, heart failure, stroke, and hypertension. In addition to the composite outcome, each subgroup of CVD was evaluated separately. All CVDs were defined by hospital diagnosis codes in the DNPR.

4.6 Covariates

Information on various covariates was retrieved to enable characterization of the study population (Studies I-IV), stratification (Studies I-IV), standardization (Study III), and confounder adjustment through multivariable regression (Studies III-IV). Covariates including age, sex, place of residence, and civil status was retrieved from the CRS.[155] Information on comorbidities and medical and surgical procedures, including kidney transplantation and KRT, was obtained from the DNPR.[154] Information on prescription drug use was obtained from the NPR[156] and information on contacts and procedures performed in the primary healthcare sector was retrieved from the NHSR (Studies I and III).[157]

In addition to individual comorbidities, the Charlson Comorbidity Index (CCI) score was used to categorize overall comorbidity in Study III.[163] The coding of the included conditions has been found to have a high positive predictive value (PPV) in the DNPR.[164]

In Studies II-IV, we stratified AKI episodes by the highest reached AKI stage based on changes in pCr or initiation of KRT within seven days of AKI onset in accordance with the KDIGO definition (Table 1).[1] In Studies II-IV, AKI was categorized as community-acquired if it occurred on a day without hospitalization or on the first day of hospitalization and as hospital-acquired if it occurred after the first day of hospitalization.[90] In Study IV, we additionally defined AKI occurring more than one day after admission to an ICU as ICU-acquired AKI. In Studies II and IV, AKI was categorized as surgery-related if it occurred within seven days after surgery and as sepsis-related if it occurred during a hospitalization with a registered code for a sepsis diagnosis (categories were not mutually exclusive).

In Study III, additional analyses were performed according to categories of municipalities as defined by Statistics Denmark.[165] The classification defines five municipality categories based on a composite of the number of residents in the largest city in the municipality and the availability of jobs. The categories include capital municipalities (>200,000 available jobs), metropolitan municipalities (<200,000 available jobs and >100,000 residents in the largest city), provincial municipalities (<200,000 available jobs and 30,000-100,000 residents in the largest city), commuter municipalities (40,000-200,000 available jobs and <30,000 residents in the largest city), and rural municipalities (<40,000 available jobs and <30,000 residents in the largest city).

4.7 Statistical analysis

Analyses were performed using R versions 4.0.4-4.2.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) and SAS version

9.4 (SAS Institute, Cary, NC, USA). Data for all studies were stored and analyzed on secure servers hosted by the Danish Health Data Authority.

4.7.1 Patient characteristics

Patient characteristics including age, sex, comorbidities, prescription drug use, and information on baseline pCr and eGFR level were tabulated in contingency tables and summarized as medians with interquartile ranges (IQR) for continuous variables and counts with percentages for categorical variables (Studies I-IV).

4.7.2 Timing of complete reporting to laboratory databases (Study I)

The visual evaluation of reporting to the laboratory databases was supported by a quantitative analysis. This analysis defined the time of completion for each municipality as the month in, and after, which ≥8% of patients with diabetes residing in the municipality had a monthly pCr test (except for July, which is the primary month of summer vacation in Denmark). This is equivalent to all patients with diabetes having at least one annual pCr test, which reflects current testing guidelines in Denmark.[166-170] If the quantitative analysis identified a later time point of complete coverage than the visual inspection, data were reassessed and a consensus was reached among the authors of the study.

4.7.3 Analysis of clustered data (Study II)

Conventional statistical methods assume that observations are independent, i.e., that the value of one observation is not influenced by the value of another observation.[171] In the case of repeated measures from the same patient, this assumption is violated as the values from one patient will tend to be more similar than values from different patients.[171] The clustering of data needs to be accounted for in the analyses, which can be achieved by estimating summary measures for each cluster.[171] In Study II, each patient represented a cluster of outpatient eGFR measurements, and summary statics for each patient was estimated by fitting individual linear regressions. Specifically, eGFR was modeled as a function of time for each patient using one linear regression based on tests more than seven days before AKI and another linear regression based on tests more than 90 days after AKI (Figure 4). eGFR levels at the time of AKI were computed by extrapolating the two linear regressions to the time of AKI. For each patient, the change in eGFR level was defined as the extrapolated eGFR level at the time of AKI, from the regression using data after AKI, minus the extrapolated eGFR level at the time of AKI, from the regression using data before AKI. The relative change in eGFR level was defined as the change in eGFR level divided by the extrapolated eGFR level at the time of AKI from the regression using data before AKI, and the change in eGFR slope was

defined as the slope of the regression after AKI minus the slope of the regression before AKI. Model assumptions were checked and found appropriate using diagnostic plots of the residuals. As a visual supplement, cubic splines were used to plot the median eGFR with IQR as a function of time before and after AKI.

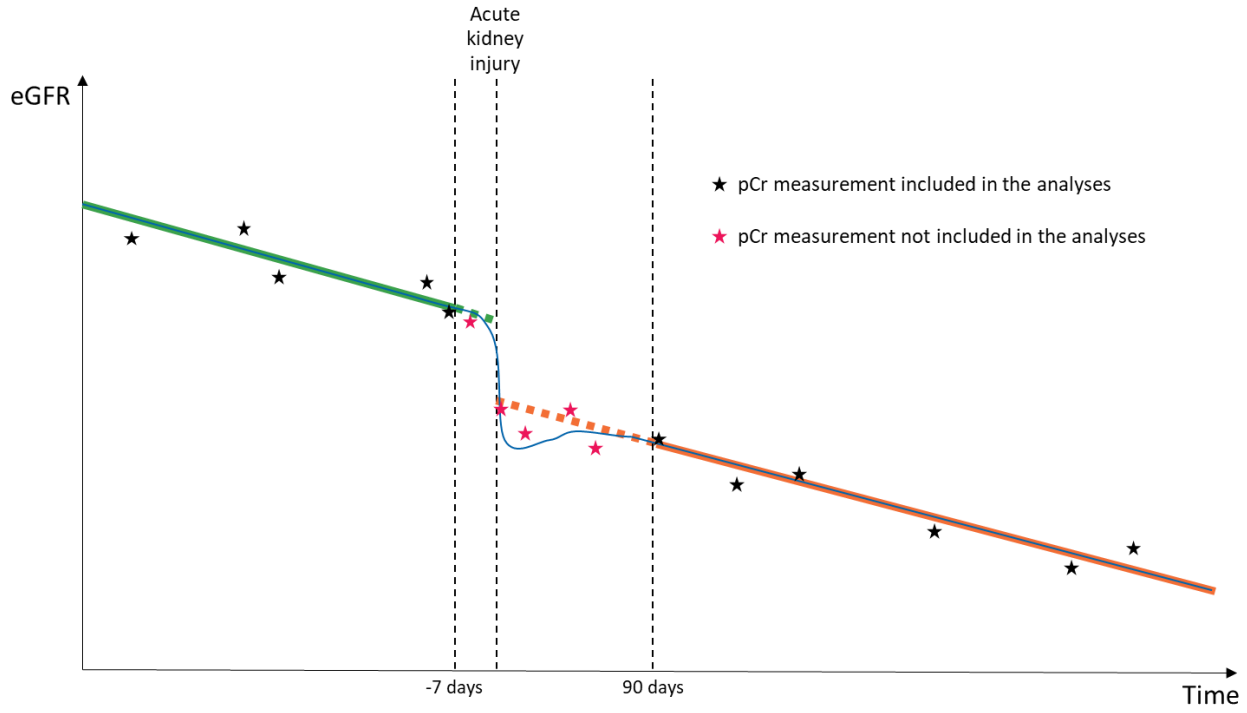

Figure 4. Modelling eGFR as a function of time before and after AKI. A hypothetical continuously measured eGFR trajectory is represented by the blue line. The solid green line represents the eGFR trajectory before AKI and the dotted green line the extrapolated eGFR trajectory from the period before AKI. The solid orange line represents the eGFR trajectory after AKI and the dotted orange line the extrapolated eGFR from the period following AKI. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Gammelager H, Birn H, Nitsch D, Christiansen CF. Kidney function before and after acute kidney injury: a nationwide population-based cohort study. Clin Kidney J. 2022 Nov 18;16(3):484-493. doi: 10.1093/ckj/sfac247* (Appendix II)[172]. Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

4.7.4 Incidence rates and standardization (Study III)

Incidence rates and mortality rates express the number of events per person per unit of time and are estimated by dividing the number of events in the population with the total population-time at risk during the follow-up period.[171,173] Often, this is presented as events per person-year. In Study III, we estimated incidence rates of AKI among residents in each of the Danish regions and 1-year incidence rates of CKD and mortality among patients with AKI. The incidence rates of AKI were estimated using the number of adult residents on 1 January 2017 by region assuming that each person contributed one year of person-time.[159]

In addition to crude incidence rates, we estimated sex-and-age-standardized incidence rates.[171] Direct standardization by sex and age is performed by applying sex and age-specific rates to a standard population.[171] When standardizing the AKI incidence rates, the adult Danish population on 1 January 2017

was used as the standard population, while the CKD-free AKI population was used for standardization of the CKD rates, and the overall AKI population was used for standardization of the mortality rates. The resulting standardized rates allow for a comparison of results across regions despite differences in sex and age distributions. Confidence intervals (CI) were computed using the approximate bootstrap method.[174]

4.7.5 Cumulative incidence (Study IV)

In Study IV, we evaluated the cumulative incidences (risks) of CKD and CVD after AKI using the Aalen-Johansen estimator.[175] As CKD and CVD are non-fatal events, their occurrence can be precluded by death.[176] Therefore, it is important to account for the competing risk of death when studying non-fatal outcomes.[176,177] In contrast to the widely used Kaplan-Meier estimator,[178] the Aalen-Johansen estimator allows for competing events by estimating the probability of the outcome of interest before a given time and before the competing event.[176,177] Accordingly, we used the Aalen-Johansen estimator to estimate the risks of CKD and CVD after AKI.

4.7.6 Cox proportional hazards regression (Studies III-IV)

In Studies III and IV, we used Cox proportion hazards regression to estimate crude and adjusted hazard ratios (HRs).[179] The hazard rate at a given time is the instantaneous rate of occurrence of the event of interest in subjects at risk at that time, and the HR is the ratio between hazard rates of exposure groups (or other independent variables) at any given time.[176] Central to the use of HRs is the assumption of proportional hazards over time, i.e., the HR does not depend on the time since the start of follow-up. This assumption was checked using log(-log) plots or plots of Schoenfeld residuals and found appropriate in all studies.

4.8 Ethical considerations

The four studies included were reported to the Danish Data Protection Agency (record number 2015–57-0002) by registration at Aarhus University (record number 2016–051-000001/812). According to Danish law, register-based observational studies that do not include human biological material and are based on data such as numbers, letters, and signs do not require approval from the Danish Scientific Ethics Committee.[180]

Table 6. Overview of material and methods

	Study I	Study II	Study III	Study IV
Aims	1) To identify when municipalities and regions were covered by LABKA and/or the RLRR 2) To describe the characteristics of pCr-tested individuals and the general population 3) To assess the annual proportion of Danish residents with a recorded pCr test	To describe the changes in eGFR level and eGFR slope from before to after AKI	To examine regional variation in: 1) AKI incidence 2) CKD, mortality, and follow-up after AKI	To examine whether AKI duration is a risk factor for CKD and CVD in a population-based setting
Study period	1 Jan 1990 - 31 Dec 2018	1 Apr 2010 - 31 Dec 2017 with follow-up through 2018	1 Jan 2017 - 31 Dec 2017 with follow-up through 2018	1 Jan 1990 - 31 Dec 2018
Design	Population-based cohort study	Population-based cohort study	Population-based cohort study	Population-based cohort study
Data sources	CRS, LABKA, RLRR, DNPR, NPR, NHSR, Danish National Pathology Registry, StatBank Denmark	CRS, LABKA, RLRR, DNPR, NPR	CRS, RLRR, DNPR, NPR, StatBank Denmark	CRS, LABKA, RLRR, DNPR, NPR
Study population	Individuals with a pCr test and a random sample of the general population (all ages)	Patients (≥18 years) with AKI and ≥3 outpatient pCr tests before and after AKI	1) Individuals (≥18 years) 2) Patients (≥18 years) with AKI	Patients (≥18 years) with AKI and an outpatient baseline pCr test and assessment of AKI duration within the first seven days after AKI
Exposures	1) Calendar month and year 2) Descriptive (no exposure) 3) Calendar year	Time before and after AKI	Region of residence	AKI duration: Rapid reversal AKI (<48 hours), persistent AKI (2-7 days), AKD (>7 days)
Outcomes	1) Complete geographical coverage on a municipal and a regional level 2) Characteristics of the two cohorts 3) Annual proportion of individuals with a pCr test	- eGFR levels and slopes before and after AKI - Changes in eGFR levels and slopes from before to after AKI	1) AKI 2) CKD, mortality, biochemical follow-up, and outpatient contact with a nephrology department following AKI	CKD, kidney failure, CVD (overall and by subtypes)
Covariates[1]	Age, sex	Age, sex, baseline eGFR, AKI stage, location, setting, calendar period	Age, sex, selected comorbidities and prescriptions, markers of lifestyle, baseline eGFR	Age, sex, selected comorbidities and prescriptions, markers of lifestyle, baseline eGFR, AKI stage, location, setting

Statistical analysis	- Daily and annual counts of pCr tests by municipality, annual counts of pCr tests by region, annual proportion of individuals with a pCr test by region - Complete geographical coverage was defined as the timepoint when daily counts of recorded pCr tests from each municipality became stable by visual inspection	Analyses of clustered data by summary measures (individual linear regressions)	Crude and standardized incidence rates, Cox regression	Cumulative incidence, Cox regression
Additional analysis	Assessment of the time of complete geographical coverage was supported by quantitative analyses of when at least 8% of patients with diabetes within a municipality had a monthly pCr test	- Stratification by age groups, baseline eGFR, calendar period, AKI stage, location, and setting - Repeating main analyses including patients with two tests before and after AKI - Proportion of patients with a rapid decline in eGFR defined as a decline of >5 ml/min/1.73 m^2/year before and after AKI	Analyses were repeated according to municipality categories	- Stratification by age groups, sex, baseline eGFR, AKI stage, location, and setting - Repeating main analyses including patients with baseline within 90 days before AKI and restricting to AKI after 1 April 2010

[1]Covariates used for stratification, standardization, and multivariable regression.

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CRS, Civil Registration System; CVD, cardiovascular disease; DNPR, Danish National Patient Registry; eGFR, estimated glomerular filtration rate; LABKA, Clinical Laboratory Information System Research Database; NHSR, The National Health Service Registry, NPR, Danish National Prescription Registry; pCr, plasma creatinine; RLRR, Register of Laboratory Results for Research.

5. Results

The main findings from the four studies comprising this dissertation are outlined in the following sections. For a more detailed description, please see the full versions of Studies I-IV included in the corresponding Appendices I-IV.

5.1 Routine clinical care creatinine data in Denmark (Study I)

The study population included 4,647,966 Danish individuals, who had one or more pCr tests recorded in LABKA or the RLRR during 1990-2018. During the study period, a total of 61,011,941 pCr tests were recorded.

The annual recording of pCr tests increased steadily during the 2000s and 2010s for regions reporting to LABKA (the North Denmark Region and the Central Denmark Region). For regions reporting solely to the RLRR (the Capital Region of Denmark, the Region of Southern Denmark, and Region Zealand) there was a steep increase in the annual number of recorded pCr tests at the onset of reporting to the database (Figure 5).

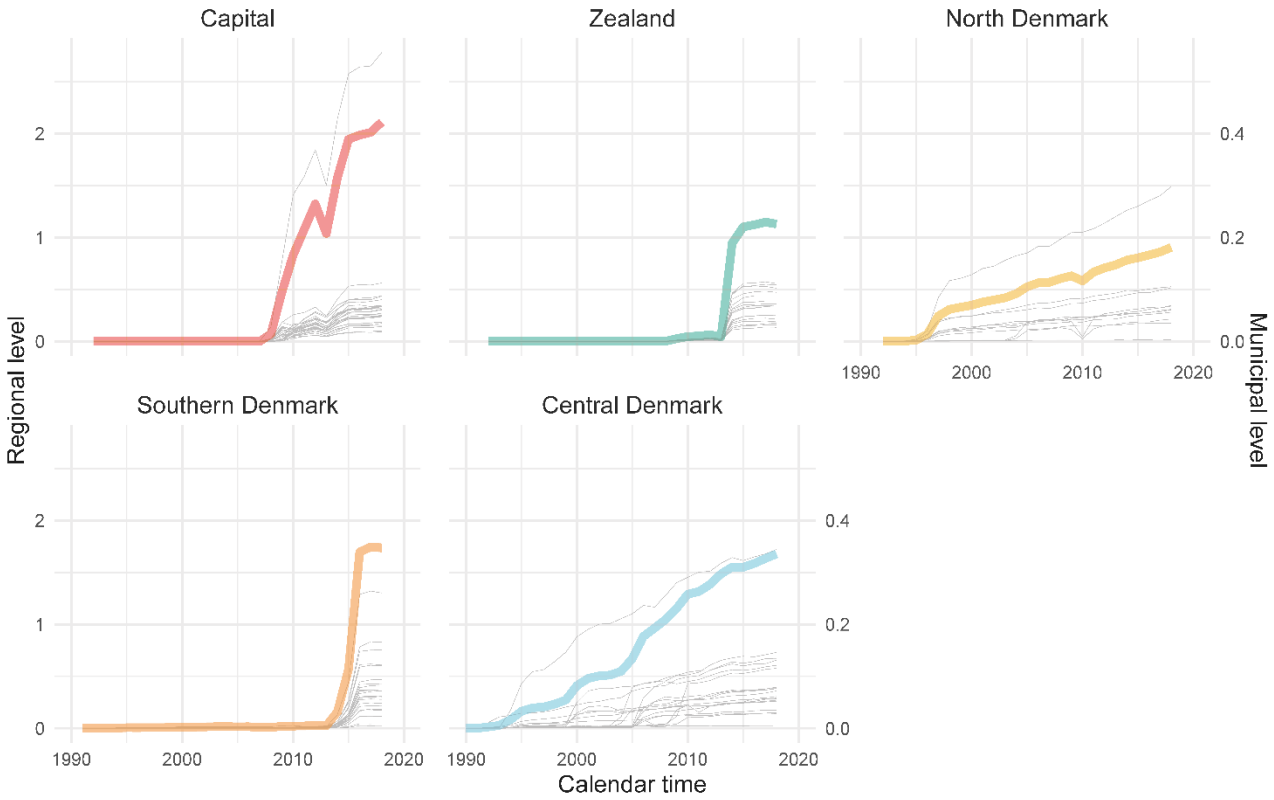

Figure 5. The recording of pCr tests (annual number in millions) in Danish regions and municipalities. Each panel covers one region with the colored line representing the overall number of tests in the region and the gray lines representing municipalities within that region. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Sørensen HT, Christiansen CF. Routine Clinical Care Creatinine Data in Denmark - An Epidemiological Resource for Nationwide Population-Based Studies of Kidney Disease. Clinical epidemiology. 2022;14:1415-1426. doi:10.2147/CLEP.S380840,* (Appendix I)[160]. Abbreviations: pCr, plasma creatinine.

The two regions reporting to LABKA were the first to achieve complete geographical coverage. The North Denmark Region achieved complete coverage in November 2004 and the Central Denmark Region in November 2009. For the three regions reporting solely to the RLRR, the Capital Region of Denmark had complete geographical coverage in October 2014, the Region of Southern Denmark in October 2015, and Region Zealand in February 2014 (Figure 6).

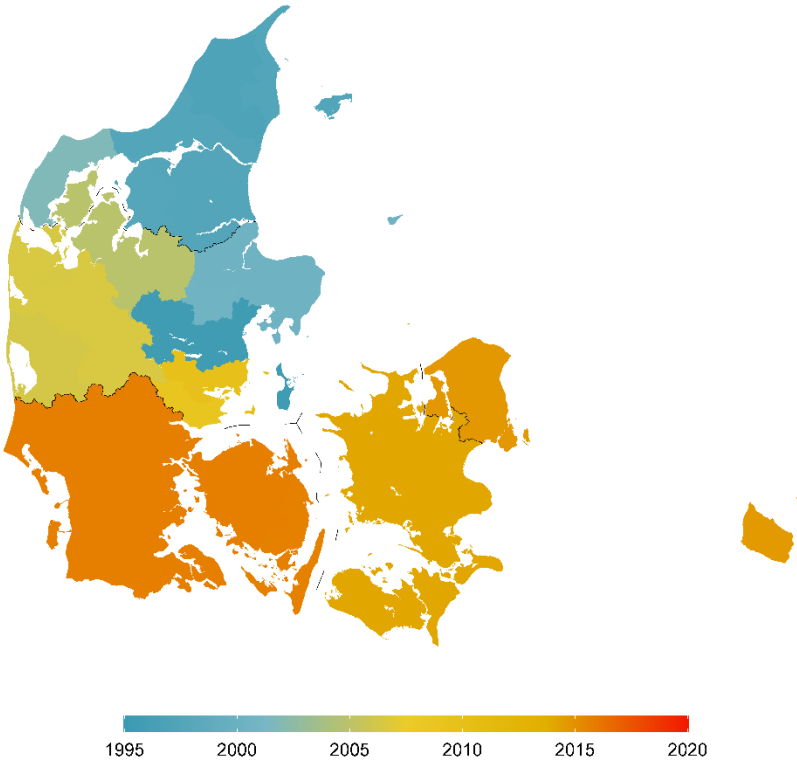

Figure 6. Map of Denmark illustrating the time of complete geographical coverage by municipality. Color temperature represents the time of complete coverage. Black lines mark the regional borders. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Sørensen HT, Christiansen CF. Routine Clinical Care Creatinine Data in Denmark - An Epidemiological Resource for Nationwide Population-Based Studies of Kidney Disease. Clinical epidemiology. 2022;14:1415-1426. doi:10.2147/CLEP.S380840,* (Appendix I)[160].

During the 2016-2018 period, where nationwide coverage was complete, 22,186,849 pCr tests were recorded from 3,403,441 unique Danish individuals. Compared with a random sample of the general population, pCr-tested individuals were more often females (54% versus 50%), older (53 versus 41 years), had more comorbidities, and used more prescription drugs. Detailed characteristics of pCr-tested individuals and a random sample of the general population can be found in Appendix I, Table 1. In this period, each year more than one in three Danish residents had a pCr test. The annual proportion of individuals with a pCr test increased with age to a maximum of 94%-96% among those aged 77-87 years. For children and individuals >60 years of age the proportion of pCr-tested individuals were similar for men

and women. However, from early adolescence until approximately 60 years of age, the proportion of women with a pCr-test was higher than among men.

5.2 Kidney function before and after acute kidney injury (Study II)

From 1 April 2010 to 31 December 2017, we identified 265,161 patients with a first-time laboratory-recorded AKI. Of these, 98,072 had three or more outpatient pCr tests before and after AKI and were included in the analyses. Included patients were younger and had more comorbidities compared with patients not included. Among the included patients, 64,805 (66%) had a baseline eGFR ≥60 ml/min/1.73 m^2 and 33,267 (34%) had a baseline eGFR <60 ml/min/1.73 m^2. The main analyses were conducted according to these two cohorts. Detailed characteristics of patients included and not included in the analyses can be found in Appendix II, Table 1 and S1.

In both cohorts, median eGFR decreased in the period leading up to AKI and drastically dropped at the time of AKI (Figure 7). Following AKI, median eGFR increased rapidly but did not return to the level before AKI before transitioning to a steady decrease.

For patients with a baseline eGFR ≥60 ml/min/1.73 m^2, the median difference in absolute eGFR level from before to after AKI was -5.6 ml/min/1.73 m^2 (IQR, -16.1 to 1.8), the median relative change in eGFR level was -6.1% (IQR, -18.5 to 2.1), and the median difference in eGFR slope from before to after AKI was -0.4 ml/min/1.73 m^2/year (IQR, -5.5 to 4.4) (Figures 7 and 8).

For patients with a baseline eGFR <60 ml/min/1.73 m^2, the median difference in absolute eGFR level from before to after AKI was -2.2 ml/min/1.73 m^2 (IQR, -9.2 to 4.3), the median relative change in eGFR level was -5.5% (IQR, -21.3 to 11.0), and the median difference

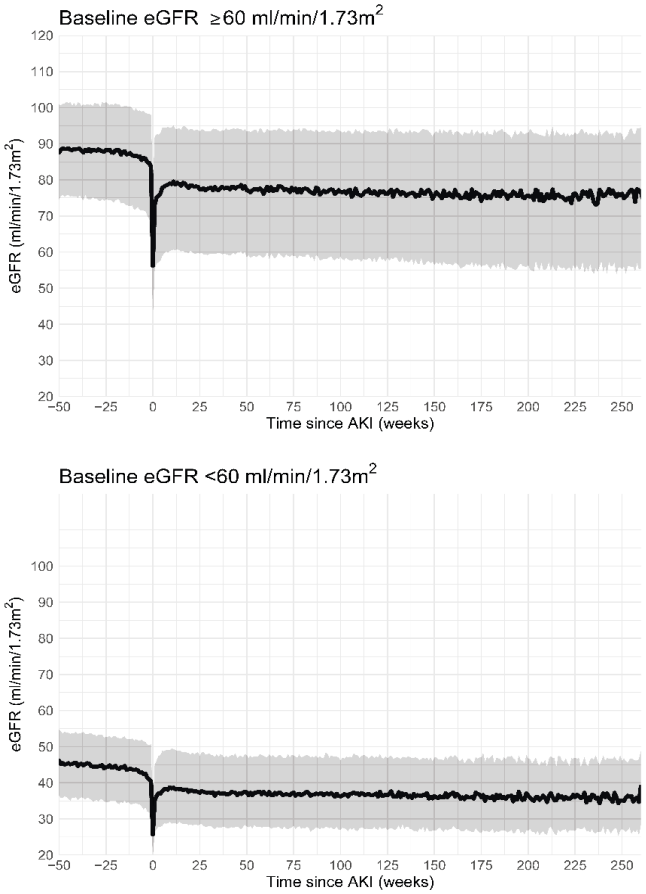

Figure 7. eGFR (median (black line) with IQR (grey area)) according to time before and after AKI. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Gammelager H, Birn H, Nitsch D, Christiansen CF. Kidney function before and after acute kidney injury: a nationwide population-based cohort study. Clin Kidney J. 2022 Nov 18;16(3):484-493. doi: 10.1093/ckj/sfac247* (Appendix II)[172]. Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

in eGFR slope from before to after AKI was 1.5 ml/min/1.73 m^2/year (IQR, -2.9 to 6.5) (Figures 7 and 8). These findings were consistent with a sensitivity analysis of patients with two or more pCr tests before and after AKI. Furthermore, the pattern of changes in eGFR level and eGFR slope from the main analysis was consistent across AKI stages, location (community and hospital), setting (sepsis and surgery), age groups (<40, 40-59, 60-79, and ≥80 years), and calendar periods (2010-2013, 2014-2015, and 2016-2017).

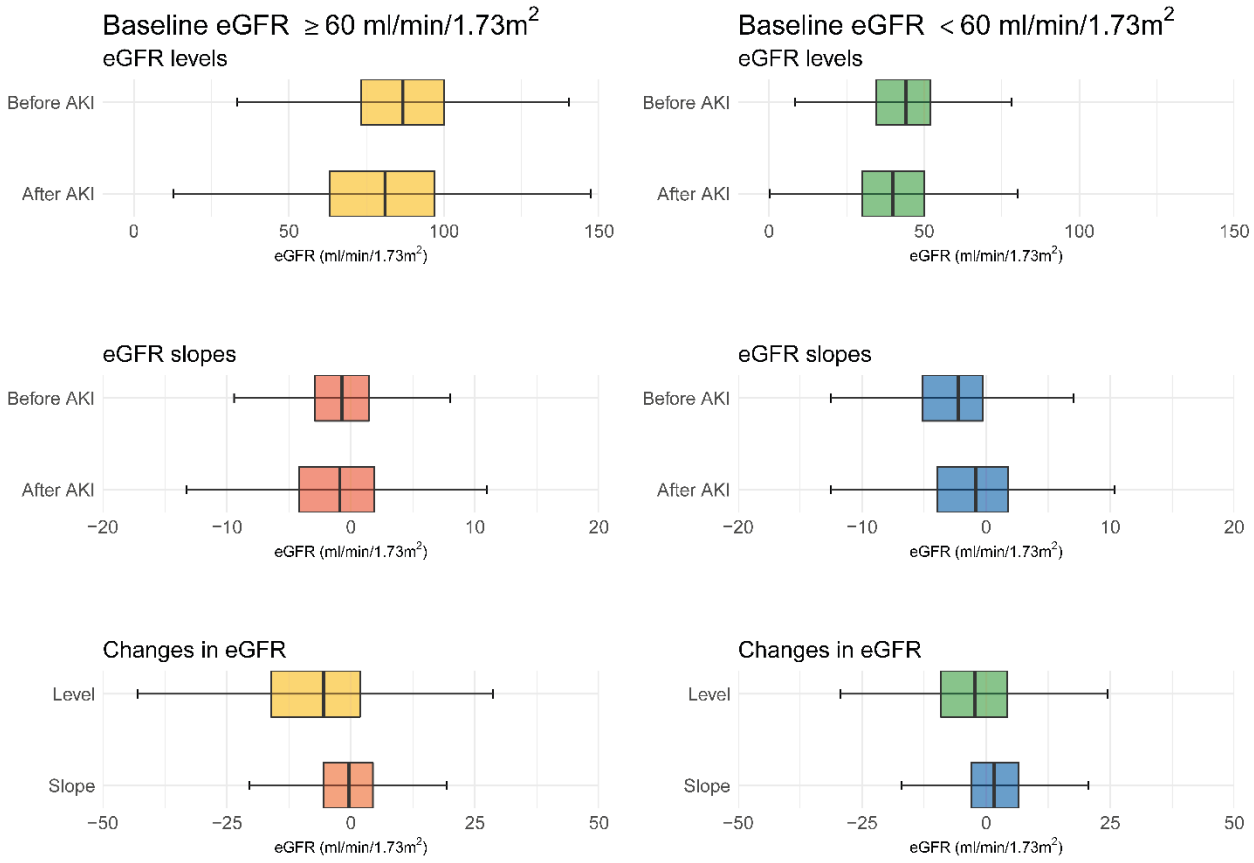

Figure 8. Distributions of extrapolated eGFR levels and eGFR slopes before and after AKI by baseline eGFR. From *Jensen SK, Heide-Jørgensen U, Vestergaard SV, Gammelager H, Birn H, Nitsch D, Christiansen CF. Kidney function before and after acute kidney injury: a nationwide population-based cohort study. Clin Kidney J. 2022 Nov 18;16(3):484-493. doi: 10.1093/ckj/sfac247* (Appendix II)[172]. Abbreviations: eGFR, estimated glomerular filtration rate.

5.3 Regional variation in incidence and prognosis of acute kidney injury (Study III)

We identified 63,382 AKI episodes in 58,356 adults in 2017. Overall, patient characteristics were similar across regions (Appendix III, Table 1). Still, residents of Region Zealand had slightly more comorbidities, while the Capital Region of Denmark had slightly fewer users of most prescription drugs.

5.3.1 Incidence of acute kidney injury

The crude AKI incidence rates ranged from 13.0 to 15.9 per 1,000 person-years across regions, while sex-and-age-standardized rates ranged from 12.9 to 14.9 per 1,000 person-years (Figure 9).

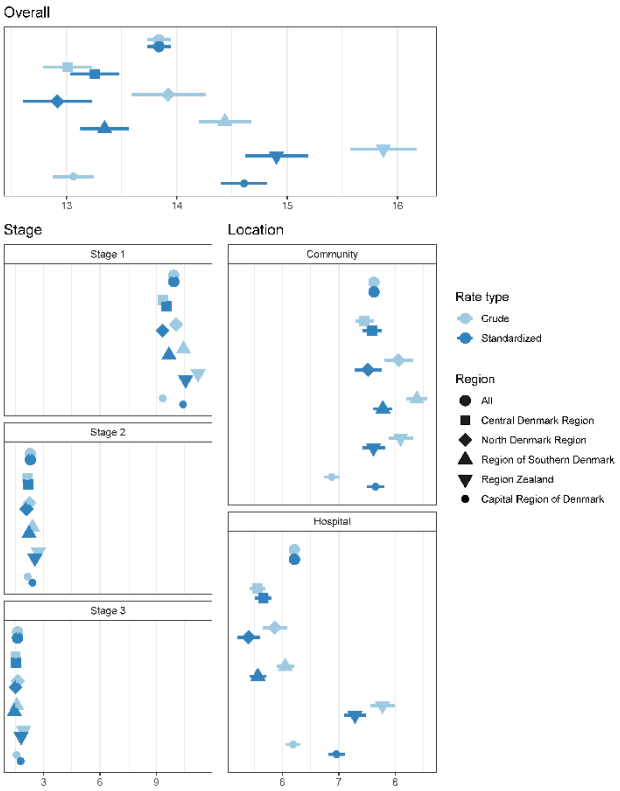

Figure 9. Incidence rates of AKI. Symbols indicate the point estimates and lines indicate the 95% confidence intervals. All x-axes display incidence rates per 1,000 person-years. From *Jensen SK, Rasmussen TB, Jacobsen BH, Heide-Jørgensen U, Sawhney S, Gammelager H, Birn H, Johnsen SP, Christiansen CF. Regional variation in incidence and prognosis of acute kidney injury in Denmark: a population-based cohort study* (Appendix III). Abbreviations: AKI, acute kidney injury.

5.3.2 Chronic kidney disease, mortality, and follow-up after acute kidney injury

The standardized 1-year incidence rates of CKD after AKI ranged from 124 to 144 per 1,000 person-years. After adjusting for differences in patient characteristics, the North Denmark Region had the highest adjusted hazard ratio (aHR) of CKD after AKI [HR: 1.25 (95% CI, 1.12-1.40) compared with the Capital Region of Denmark] (Table 7).

Standardized 1-year mortality rates after AKI ranged from 337 to 381 per 1,000 person-years, while the aHRs of death were comparable across regions (Table 7).

The proportion of patients with biochemical follow-up including urine dipstick tests and measurements of urine albumin, urine albumin-creatinine ratio, and pCr within three months after AKI ranged from 60% to 69% across regions. Similarly, outpatient contact with a nephrology department among patients with KRT-requiring AKI was between 25% and 32%. The Capital Region of Denmark had a slightly lower aHR of biochemical follow-up than the other regions, while the Central Denmark Region had the highest aHR of outpatient nephrology follow-up among patients with KRT-requiring AKI (Table 7).

When examining CKD, mortality, and follow-up after AKI according to municipality categories, the aHRs of death were similar, while the rural municipalities had the highest aHR of CKD [HR 1.14 (95% CI, 1.04-1.25)]. Furthermore, the aHR of biochemical follow-up was slightly lower in the capital municipalities than the other municipality categories, and the aHR of outpatient nephrology follow-up among patients with KFT-requiring AKI were lower in rural and capital municipalities than in commuter, provincial, and metropolitan municipalities.

Table 7. Adjusted hazard ratios for chronic kidney disease, death, biochemical follow-up, and outpatient contract with a nephrology department after acute kidney injury

	Central Denmark Region	North Denmark Region	Region of Southern Denmark	Region Zealand	Capital Region of Denmark
Chronic kidney disease	1.03 (0.94-1.13)	1.25 (1.12-1.40)	1.11 (1.01-1.21)	1.07 (0.97-1.18)	1 (ref)
Death	0.99 (0.94-1.04)	1.05 (0.99-1.11)	1.02 (0.98-1.07)	1.05 (1.00-1.10)	1 (ref)
Biochemical follow-up[a]	1.13 (1.09-1.16)	1.14 (1.10-1.18)	1.10 (1.07-1.13)	1.08 (1.05-1.12)	1 (ref)
Outpatient contact with a nephrology department within six months after AKI onset among KRT-requiring AKI	1.50 (0.99-2.28)	1.04 (0.64-1.70)	1.11 (0.69-1.77)	1.28 (0.85-1.94)	1 (ref)

[a]Biochemical follow-up covered any dipstick, u-albumin, UACR, or pCr test within three months after the end of an AKI episode. Models were adjusted for differences in demographics, comorbidities, medication use, lifestyle and social factors, and baseline eGFR. *From Jensen SK, Rasmussen TB, Jacobsen BH, Heide-Jørgensen U, Sawhney S, Gammelager H, Birn H, Johnsen SP, Christiansen CF. Regional variation in incidence and prognosis of acute kidney injury in Denmark: a population-based cohort study* (Appendix III). Abbreviations: AKI, acute kidney injury; KRT, kidney replacement therapy.

5.4 Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease (Study IV)

From 1 January 1990 to 31 December 2018, we identified 169,582 patients with AKI, who had an outpatient baseline pCr test within the prior 8-365 days, assessment of AKI duration by one or more pCr tests within seven days after AKI onset, and were alive and uncensored at the start of follow-up. Among included patients, 36,514 (22%) had rapid reversal AKI, 22,619 (13%) had persistent AKI, and 110,499 (65%) had AKD. Detailed characteristics of included patients can be found in Appendix IV, Table 1.

5.4.1 Chronic kidney disease and kidney failure

During the 20 years of follow-up, the risk of CKD was 18.9% (95% CI, 18.2-19.6) for rapid reversal AKI, 23.2% (95% CI, 22.1-24.2) for persistent AKI, and 22.0% (95% CI, 21.6-22.5) for AKD (Figure 10). The aHR for CKD increased with AKI duration [aHR = 1.15 (95% CI, 1.09-1.22) for persistent AKI and 1.47 (95% CI, 1.40-1.53) for AKD compared with rapid reversal AKI].

The risk of kidney failure during the 20 years of follow-up was 1.8% (95% CI, 1.6-2.0) for rapid reversal AKI, 2.4% (95% CI, 2.1-2.7) for persistent AKI, and 2.6% (95% CI, 2.5-2.7) for AKD (Figure 10). The aHR was 1.09 (95% CI, 0.94-1.26) for persistent AKI and 1.50 (95% CI, 1.33-1.66) for AKD compared with rapid reversal AKI.

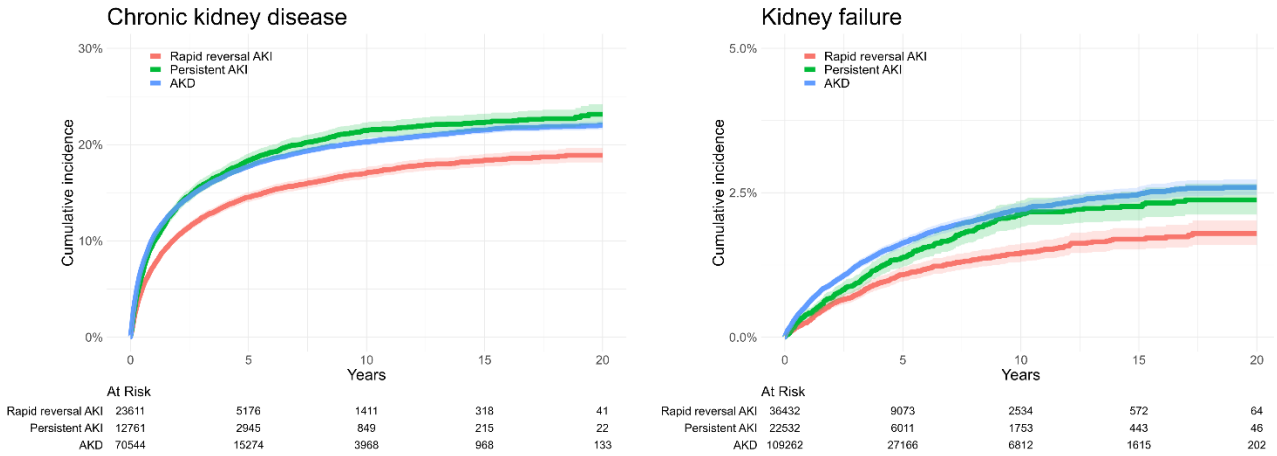

Figure 10. Twenty-year risks of chronic kidney disease and kidney failure. From *Jensen SK, Heide-Jørgensen U, Gammelager H, Birn H, Christiansen CF. Acute kidney injury duration and 20-year risk of chronic kidney disease and cardiovascular disease: a population-based cohort study* (Appendix IV). Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury.

5.4.2 Cardiovascular disease

The overall risk of CVD during the 20 years of follow-up was 37.3% (95% CI, 35.3-39.4) for rapid reversal AKI, 35.6% (95% CI, 33.9-37.3) for persistent AKI, and 33.8% (95% CI, 32.9-34.7) for AKD (Figure 11). The aHR for CVD was comparable across AKI duration groups [aHR = 1.02 (95% CI, 0.95-1.09) for persistent AKI and 0.98 (95% CI, 0.93-1.03) for AKD compared with rapid reversal AKI]. This was consistent for outcomes of atrial fibrillation or flutter, stroke, and hypertension. For ischemic heart disease, the aHR was slightly higher for AKD than rapid reversal AKI [aHRs = 1.11 (95% CI, 1.03-1.19)], while both persistent AKI and AKD were associated with higher rates of heart failure [aHRs = 1.09 (95% CI, 1.02-1.16) and 1.09 (95% CI, 1.03-1.15), respectively] than rapid reversal AKI.

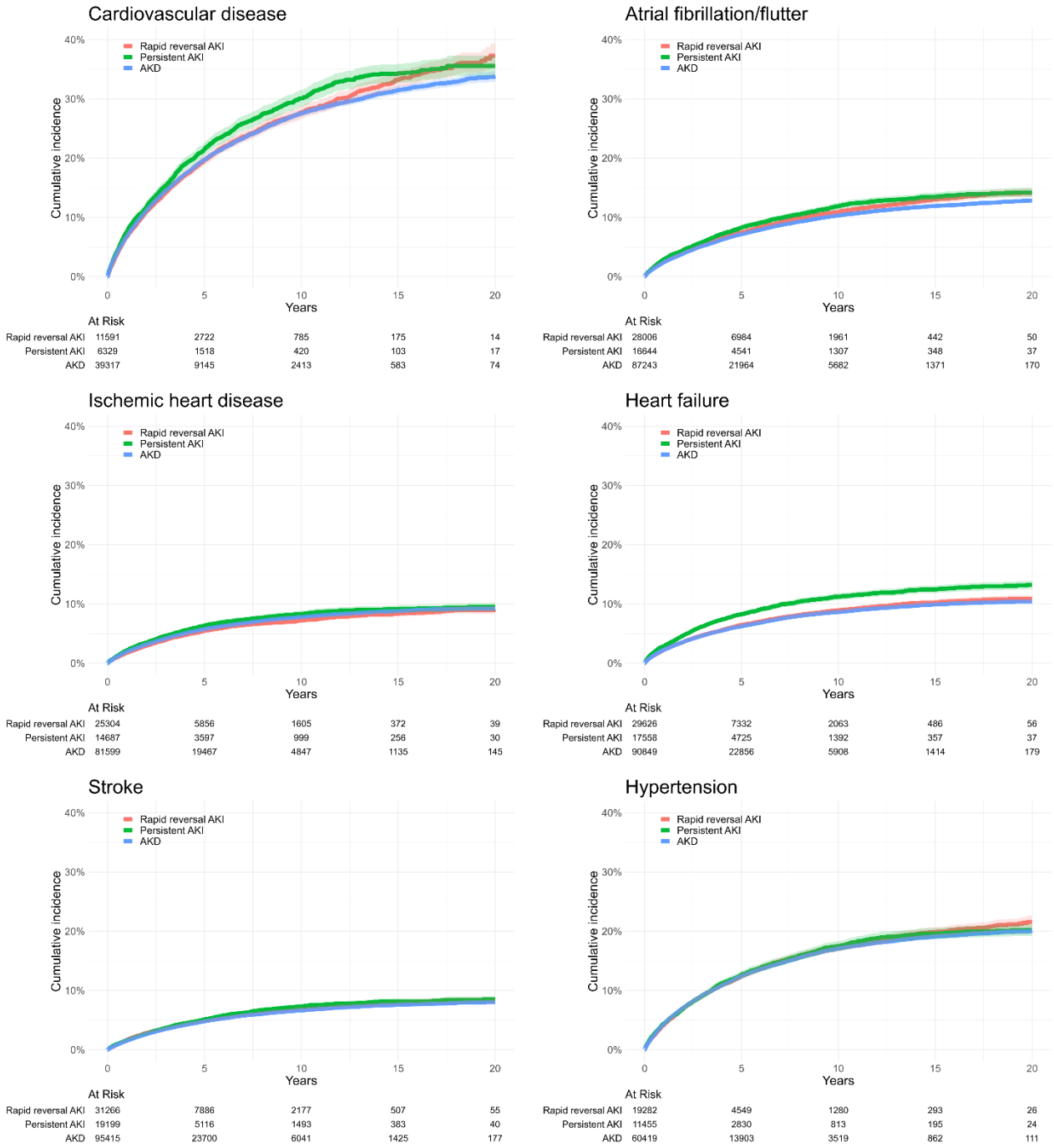

Figure 11. Twenty-year risks of cardiovascular disease. From *Jensen SK, Heide-Jørgensen U, Gammelager H, Birn H, Christiansen CF. Acute kidney injury duration and 20-year risk of chronic kidney disease and cardiovascular disease: a population-based cohort study* (Appendix IV). Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury.

6. Discussion

6.1 Main findings

In Study I, we showed that the combination of pCr data from LABKA and the RLRR offer long follow-up and nationwide coverage with the first recordings made in the 1990s, regional coverage beginning in November 2004, and complete nationwide coverage from October 2015. In recent years, more than one-third of the Danish population had a pCr test at least once a year. Tested individuals were more often females, were older, and had more comorbidities than the general population.

In Study II, we found that AKI was associated with long-term changes in eGFR level and eGFR slope in patients with repeated outpatient pCr tests before and after AKI. For the main cohorts (baseline eGFR ≥ or <60 ml/min/1.73 m^2), AKI was associated with a drop in eGFR level when comparing the period after AKI to the period before AKI. Furthermore, AKI was associated with a decrease in eGFR slope in the cohort with baseline eGFR ≥60 ml/min/1.73 m^2, while an increase in eGFR slope was found in the cohort with eGFR <60 ml/min/1.73 m^2.

In Study III, we found regional variation in AKI incidence rates, which was partially attributable to differences in age and sex distributions across the Danish regions. The mortality after AKI was similar after adjusting for differences in patient characteristics. However, CKD, biochemical follow-up, and outpatient contact with a nephrology department after KRT-requiring AKI varied across regions. Similar differences were found across categories of municipalities.

In Study IV, we found a gradual increase in rates of CKD and kidney failure with increasing AKI duration. AKI duration was not associated with rates of overall CVD. However, AKD was associated with a slightly higher rate of ischemic heart disease than rapid reversal AKI, while both persistent AKI and AKD were associated with a minor increase in rates of heart failure compared rapid reversal AKI.

6.2 Comparison with the existing literature

6.2.1 Routine clinical care creatinine data in Denmark (Study I)

The overall findings on population coverage and characteristics of pCr-tested individuals from Study I correspond to findings from other studies on population-based laboratory databases with pCr data.[109-112] Kampmann et al.[111] reported that 78% of adult residents in the included municipalities had a pCr test during 2007-2013. Correspondingly, Henriksen et al.[110] reported a population coverage of 66% among all residents on Funen during 2000-2015. The lower population coverage reported by Henriksen et al.[110] is likely related to the inclusion of individuals <18 years, which we found to be the age group with the lowest proportion of

tested individuals. Similar to our findings, three studies reported that around one-third of residents had a sCr test each year.[110-112]

The annual proportion of individuals with a pCr test increased steadily for all regions after archiving complete geographical coverage. A similar observation was reported by Henriksen et al.[110] None of the studies describing databases with population-based sCr data had information on the cause of individual pCr tests. However, the increasing use of pCr-testing is likely related to both the increasing prevalence of noncommunicable diseases such as hypertension (from 18% in 2010 to 21% in 2021) and diabetes (5% in 2010 to 6% in 2021) and modern treatment guidelines for these diseases recommending regular biochemical testing to evaluate secondary kidney involvement and assess treatment goals.[181,182]

We found a higher proportion of females than males among pCr-tested individuals. The discrepancy was most pronounced from adolescence to approximately 60 years of age. Runesson et al.[111] observed a similar difference in pCr testing in this interval and other studies also reported a higher proportion of females among tested individuals compared with the general population.[110,112] This could be related to gender differences in healthcare-seeking behaviors and consultations for reproductive reasons as differences in primary care consultations, especially during the reproductive years, closely resemble the differences in pCr testing.[183,184]

Our findings complement previous studies describing the structure and content of LABKA and the RLRR.[150,151] Information on the geographical coverage of the databases will facilitate studies based on these data by providing information that enables optimization of the study period when complete geographical coverage is required, such as in Study III. In addition, this will be of relevance to studies on temporal trends of kidney diseases based on pCr tests both to assure that findings are not due to incomplete data but also to account for temporal changes in testing frequencies. Finally, although we only examined the geographical coverage of pCr tests, we would expect the findings to apply to the databases in general, i.e., other biomarkers are likely to follow a similar pattern of reporting to the databases.

6.2.2 Kidney function before and after acute kidney injury (Study II)

Utilizing Danish pCr data, we extend findings from smaller studies on selected patient populations by providing data on the association between AKI and changes in eGFR in population-based cohorts. In the cohort with a baseline eGFR <60 ml/min/1.73 m^2, we found a median difference in eGFR level of -2.2 ml/min/1.73 m^2 (IQR, -9.2 to 4.3) from before to after AKI. D'Hoore et al.[119] also reported a drop in eGFR level from before to after AKI among 331 patients with CKD. However, they found a difference in eGFR level of -11 ml/min/1.73 m^2 (IQR, -22 to 0).[119] In our study, the size of the absolute drop in eGFR level decreased

with baseline eGFR. This may explain some of the disparity between our findings and the findings of D'Hoore et al.[119] as their cohort had a higher baseline eGFR than our cohort (median eGFR 46 ml/min/1.73 m^2 versus 55 ml/min/1.73 m^2). Nonetheless, findings on changes in eGFR level from studies including patients with CKD generally lack consistency and other studies reported no change[121] or even a rise in eGFR level following AKI.[117]

In addition to the drop in eGFR level, we found a lower rate of eGFR decline after AKI compared with before among patients with a baseline eGFR <60 ml/min/1.73 m^2. Similarly, D'hoore et al.[119] reported a change from a median decline of 5 ml/min/1.73 m^2/2.5 years (IQR, 0-13) before AKI to 1 ml/min/1.73 m^2/2.5 years (IQR, 2-6) after AKI in patients with CKD. However, based on a similar cohort of patients with CKD, an American study[121] reported no changes in eGFR from one year before to five years after AKI, while other studies[117,118] reported a decrease in eGFR slope from before to after AKI.

To our knowledge, we are the first to report on changes in eGFR level and eGFR slope from before to after AKI in a population-based cohort of patients with a baseline eGFR ≥60 ml/min/1.73 m^2. We found a drop in eGFR of -5.6 ml/min/1.73 m^2 (IQR, -16.1 to 1.8) equivalent to a relative change in eGFR level of -6.1% (IQR, -18.5 to 2.1). In comparison, a study on US veterans reported a drop in eGFR level of approximately 10% following AKI.[121] Similarly, median eGFR dropped from 73 ml/min/1.73 m^2 (IQR, 51-87) before admission to 61 ml/min/1.73 m^2 (IQR, 37-96) at discharge in a cohort of ICU patients with stage 2-3 AKI.[115] However, in the same study, patients with stage 1 AKI experienced an increase in median eGFR from 73 ml/min/1.73 m^2 (IQR, 50-82) to 78 ml/min/1.73 m^2 (IQR, 56-107) during the same period.[115]

Besides the drop in eGFR level, we found a slightly higher rate of eGFR decline after AKI compared with before. Similar findings were reported for stage 2-3 AKI among patients undergoing coronary angiography with a post-angiography eGFR <90 ml/min/1.73 m^2, while patients with stage 1 AKI had similar rates of eGFR decline before and after AKI.[120] Other studies including patients without CKD compared slopes among different stages of AKI or different causes of AKI but did not include information on eGFR slope before AKI.[115,116]

Several factors could contribute to the variation in the reported associations between AKI and changes in eGFR. Whereas we defined population-based cohorts by baseline eGFR level and required repeated pCr tests before and after AKI, other studies used specific patient cohorts,[115,116,120] cohorts of CKD patients,[117-119] relied on diagnosis codes for identification of AKI,[121] or did not require sCr tests following AKI.[117,118,121] Differences in study populations, including age, comorbidities, and baseline eGFR, which are known to be associated with the risk of CKD could explain some of the variation in outcomes.[4,48] Another important factor could be discrepancies in the definitions of changes in eGFR. While we examined changes in both

eGFR level and eGFR slope some studies only examined changes in eGFR level[121] or eGFR slope[118] and for those studying both, various definitions and statistical approaches were applied.[115-117,119,120] In addition, findings might be influenced by differences in mortality following AKI, which is discussed separately in the Methodological considerations section below.

6.2.3 Regional variation in incidence and prognosis of acute kidney injury (Study III)

Regional variation in AKI incidence has been examined in studies from the UK,[124,125,127] Peru,[123] USA,[129] and China.[126,128] Findings from these studies were heterogeneous with some reporting little or no variation in regional AKI incidence[125-128] and others reporting substantial variation.[123,124,129] This could reflect actual differences in regional variation of AKI, which is not unlikely given the differences in demographics and healthcare systems across the countries where these studies were performed. In countries that span a vast geographical area, variation could also be a consequence of differences in climate and local customs, which is reflected by the differences in causes of AKI reported by Wang et al.[126] Nonetheless, the inconsistency in findings could also be related to differences in the methods used for examining AKI incidence. Regional differences in access to hospitals and registration practices could bias studies restricting to hospitalized patients[126-129] or using diagnosis codes of AKI.[123] Of note, two recent studies from the UK showed conflicting results.[124,125] The studies used similar pCr-based AKI definitions; however, one study reported regional variation across six counties of Ireland,[124] while the other found similar rates of AKI in three UK regions.[125] The incongruent findings might be related to methodological differences as Stack et al.[124] examined the AKI incidence among individuals with a prior pCr test, while Sawhney et al.[125] examined the incidence among residents using census statistics. However, this may also suggest that even countries sharing comparable healthcare systems and situated in the same geographical region of the world can exhibit dissimilarities with regard to variation in AKI incidence. Nonetheless, Sawhney et al.[125] used an approach similar to ours and reported AKI incidence rates similar to the rates found in our study.

To our knowledge, we are the first to examine regional variation in CKD and clinical and biochemical follow-up after AKI. However, four of the studies examining regional variation in AKI incidence also assessed mortality rates among patients with AKI.[126-129] In contrast to our findings, most studies reported substantial variation in mortality following AKI. Most prominently, Wang et al.,[126] reported a nearly two-fold difference in hospital mortality rates across tertiles of northern latitude in China. Equivalent to the reported variation in AKI incidence, reported differences in mortality following AKI could reflect actual differences in mortality but might be biased by the methodological limitations described above. Furthermore, most studies were descriptive and did not account for differences in patient characteristics across regions.[126,128,129] Yet, even

after accounting for differences in demographics and comorbidities, Kolhe et al.[127] reported considerable variation in mortality after KRT-requiring AKI across nine English regions, which may reflect disparities in the quality of care for patients with KRT-requiring AKI.

6.2.4 Acute kidney injury duration and risks of chronic kidney disease and cardiovascular disease (Study IV)

Our study is the first to implement both the KDIGO creatinine criteria for defining AKI and the ADQI consensus definition of AKI duration to examine the long-term associations between AKI duration and CKD and CVD in a population-based cohort. Previous studies have examined the association between AKI duration and CKD; however, most did not use fixed intervals of AKI duration and none have used the full ADQI definition. Similar to our findings, others have reported that AKI duration beyond seven days was associated with an increased rate of CKD when compared with a duration of less than seven days.[138,140,143] Additionally, our overall finding of higher rates of CKD with increasing AKI duration is consistent with findings from studies in US veterans.[141,145] Heung et al.[145] found a gradual increase in 1-year risks of CKD with increasing AKI duration (≤2, 3-10, and >10 days) when comparing with patients without AKI. Similarly, Siew et al.[141] found that increasing AKI duration (5-10, 11-30, 31-90 days) was associated with gradually higher rates of a sustained decline in eGFR or kidney failure when compared with an AKI duration of 1-4 days. In contrast to these findings, others have reported little or no association between AKI duration and CKD.[139,149] Ikizler et al.[139] performed a prospective matched cohort study including 769 hospitalized patients with AKI and 769 matched patients without AKI. All categories of AKI duration (≤1, 2-3, 4-6, >6 days) were associated with higher rates of CKD compared with no AKI. Yet, they did not find a clear increment in rates of CKD with increasing AKI duration. However, this was not the primary outcome of the study and the estimates lacked precision due to the small study population. Similarly, van Kuijk et al.[149] did not find a difference in risks of CKD when comparing durations of decline in kidney function of more or less than three days. However, they defined a decline in kidney function as a decline of >10% from baseline eGFR. In a sensitivity analysis, they examined declines in eGFR of >20%, >30%, >40%, and >50%. Declines in eGFR lasting for less than three days yielded similar risks of CKD, independent of the size of the decline, while the risks of CKD increased gradually for >10%, >20%, and >30% declines in eGFR lasting beyond three days. This could indicate that the duration of decline in eGFR is of lesser importance in very mild cases of decline in kidney function.

We did not find an association between AKI duration and overall rates of CVD, but rates of heart failure were slightly higher for persistent AKI and AKD compared with rapid reversal AKI, while rates of ischemic heart disease were higher for AKD than for rapid reversal AKI. In general, there is a scarcity of studies

examining the association between AKI duration and CVD using fixed intervals for defining AKI duration. However, AKI persisting until discharge has been associated with higher rates of heart failure in patients with myocardial infarction,[54] human immunodeficiency virus,[148] or in intensive care.[147] Similarly, Ikizler et al.[139] observed higher rates of heart failure if AKI persisted for more than one day and especially if the duration exceeded six days when compared with no AKI. In addition, Gammelager et al.[147] and Choi et al.[148] found higher rates of myocardial infarction and central and peripheral arterial disease, respectively, among patients with stage 2-3 AKI lasting beyond discharge compared with patients with recovery of kidney function before discharge.

6.3 Methodological considerations

The studies included in this dissertation are observational (non-experimental) cohort studies. A cohort is a group of individuals who share a common trait or event and are followed over time.[173] In addition to cohorts of patients with AKI (Studies II-IV), we examined laboratory database coverage (Study I) and AKI incidence (Study III) using cohorts of Danish residents. Register-based cohort studies have apparent advantages such as the inclusion of a large number of patients, which increases precision and allows for the study of rare events in a cost-effective setting.[173] Additionally, observational studies may be the only option for answering certain research questions, e.g., when examining exposures that would be unethical in experimental designs. However, the use of medical databases not designed for research comes with limitations that need to be considered. The accuracy or internal validity of observational studies pertains to the soundness of study results within the source population (i.e., the population from which the study population was sampled), while external validity describes the applicability of results outside the source population.[173] The internal validity may be undermined by random and systematic error. Random error refers to the statistical precision of the estimates. Systematic error covers selection bias, information bias, and confounding.[173] These concepts will be described briefly and considered in relation to Studies I-IV in the following sections.

6.3.1 Selection bias

Selection bias arises when the association between exposure and outcome in the study population is systematically different from that of the source population.[173] This can be caused by a selection of participants entering the study or differences in those completing the study and those lost to follow-up. For all studies, we used population-based laboratory databases, which enables a uniform collection of pCr test

results from Danish residents. In addition, we used nationwide, population-based registries with complete follow-up, which is possible due to all Danish residents being registered in the CRS.[153,155]

In Study II, the study population included patients with three or more pCr tests, spanning at least 90 days, both before and after AKI. The requirement for multiple pCr tests spanning a notable duration of time was inspired by previous studies applying similar methods.[185,186] This approach has been recommended to increase the confidence of the estimates by reducing variation stemming from a limited number of pCr tests drawn in close temporal proximity.[187] While pCr is measured routinely in most patients having a blood sample, these requirements induce a risk of selection bias as some patients with AKI are less likely to be included in the study population, e.g., patients dying shortly after AKI. The included cohort had a lower median age and was generally more comorbid and used more prescription drugs than the overall cohort of patients with AKI. Additionally, the 1-year mortality was 3% among included patients and 33% among all patients with AKI. As the severity of AKI and the rate of eGFR decline are associated with the risk of death, it could be speculated that patients with the most pronounced changes in eGFR might, to an extent less than other patients, have survived to be included in the study.[27,115,188] To examine the selection imposed by requiring three or more pCr tests before and after AKI, we performed a sensitivity analysis including patients with two or more pCr tests before and after AKI. The results of this analysis were consistent with the main analysis. However, as for the main analysis, patients still needed to survive to have repeated pCr tests following AKI. Therefore, findings from this study pertain to patients, who have repeated outpatient pCr tests before and after AKI.

In Study IV, we included patients with an outpatient baseline pCr test before AKI and a pCr test during the seven days after AKI onset to allow for assessment of AKI duration. Thereby, we induced a selection of patients with available pCr tests. However, when comparing all patients with AKI to those included in the study, we did not find substantial differences in patient characteristics. The most noticeable differences were related to location and setting, with a higher proportion of included patients experiencing AKI during hospitalization and in relation to surgery compared with all patients with AKI. This was likely due to structural differences with a higher availability of pCr tests during hospitalization and after surgery. Therefore, we would not expect a substantial difference in the association between AKI duration and CKD and CVD between the included patients and those not included.

6.3.2 Information bias

Erroneous classification of exposures and outcomes can cause information bias.[173] In relation to categorical variables, information bias is referred to as misclassification. Misclassification can be non-differential if it is

only related to either exposure or outcome and differential if it is related to both. Non-differential misclassification of a dichotomous variable will bias the association towards the null, while non-differential misclassification of a categorical variable with more than two levels and differential misclassification can cause bias both towards and away from the null.[173]

6.3.2.1 Misclassification of exposure

Studies I, II, and III used calendar time, time before and after AKI, and region of residence as exposures, respectively. Every entry into the laboratory databases is automatically labeled with a date and time, reducing the risk of misclassification. Similarly, detailed information on the place of residence is recorded in the CRS.[155]

In Study IV, the exposure was AKI duration. To enable categorization of AKI duration, we required information on baseline pCr level and one or more pCr tests in the seven days following AKI. However, rapid reversal AKI could be misclassified as persistent AKI due to a lack of testing within the first two days of AKI. Nonetheless, the risk of misclassification is considered to be low as the median number of tests in the cohort during the seven days after AKI onset was 4 (IQR, 2-6) and 83% of all patients had a test within the first two days.

6.3.2.2 Misclassification of outcomes

In Study I, we defined the time of complete municipal coverage by visual inspection of testing frequencies. Although most municipalities had a distinct transition from incomplete to complete this induces a risk of misclassification due to subjectivity. Therefore, we also applied a quantitative measure defining the time of complete coverage as the month in, and after, which ≥8% of patients with diabetes had a monthly pCr test (equivalent to when all patients with diabetes had at least one pCr test each year, which reflects current testing guidelines in Denmark[166-170]). For most municipalities, the quantitative measure was fulfilled before the time of complete coverage defined by the visual inspection. Moreover, current diabetes guidelines recommend more regular biochemical testing than in the 1990s when reporting to LABKA started. In addition, full adherence to the guidelines cannot be expected as other biochemical tests recommended to be performed annually, such as plasma low-density lipoprotein cholesterol and urine albumin concentration, were only performed in 84% and 78% of patients with diabetes in 2020-2021, respectively.[189,190] Consequently, both the visual and the quantitative assessment of complete coverage are likely to be conservative. Therefore, we may have misclassified municipalities as incomplete when coverage

was complete. This comes at the price of slightly shorter follow-up but ensures that coverage is in fact complete and that changes in coverage is not interfering with findings, e.g., when studying temporal changes in kidney diseases.

In Study II, we evaluated changes in eGFR from before to after AKI. Acute illness may affect the level of pCr due to changes in muscle mass and by inducing glomerular hyperfiltration.[91,108,191,192] To minimize overestimation of eGFR due to the effect of acute illness, we restricted to pCr tests from more than 90 days after AKI onset. However, if, e.g., a loss of muscle mass or glomerular hyperfiltration persists, this would cause an overestimation of eGFR after AKI, making our estimated reductions in eGFR level conservative.

In Study III, we examined rates of AKI across the Danish regions defining AKI by the KDIGO creatinine criteria.[1] As an outpatient baseline pCr level was not available for all residents, there is a risk of underestimating the rate of AKI. However, due to the generally high availability of pCr tests in 2017 and the 48-hour and 7-day criteria, we would expect the number of AKIs missed due to missing information on baseline pCr level to be low.

In Studies III and IV, we examined the incidence of CKD following AKI. CKD was defined using a combination of pCr tests, inpatient and outpatient hospital diagnosis codes, and hospital procedure codes.[162] As for the diagnosis and procedure codes, the accuracy of the DNPR is considered to be high and the PPV of moderate to severe renal disease is 100% (95% CI, 92.9-100).[154,164] Furthermore, the assessment of pCr after AKI was similar across regions (Study III) and AKI duration groups (Study IV). As the majority of studies on CKD, we focused on GFR categories and did not include information on albuminuria.[193] A recent Danish study showed that albuminuria testing was infrequent and that combining tests for albuminuria with tests for pCr only increased estimates of CKD prevalence slightly when compared with the use of pCr tests alone.[194] Nonetheless, this may have led to an underestimation of rates of CKD in Studies III and IV.

In Study IV, we examined the risk of CVD following AKI. CVD included atrial fibrillation and flutter, ischemic heart disease, heart failure, stroke, and hypertension defined by inpatient and outpatient hospital diagnosis codes. In general, the PPVs of CVD diagnoses recorded in the DNPR codes are high.[164,195-200] We were not able to identify studies that examined the sensitivity of diagnosis codes for atrial fibrillation or flutter, ischemic heart disease, or hypertension. However, sensitivities of 29% for heart failure and 58% for stroke have been reported.[199,201] In our studies, the low sensitivity could lead to an underestimation of the risks of the outcomes. Furthermore, the duration of AKI could be associated with the recording of CVD diagnoses as patients with a long AKI duration may have more contacts with the healthcare system in the period following AKI onset than patients with a short AKI duration. This difference in surveillance following AKI onset means that the misclassification of CVD could be related to AKI duration. Therefore, we chose to

postpone the start of follow-up to day 90 after AKI. Even so, remains possible that differences in surveillance persisted after this point in time. However, we only found increased rates of heart failure and ischemic heart disease with increasing AKI duration and not increased rates of atrial fibrillation and flutter, stroke, and hypertension, which could also have been more frequently diagnosed among patients with long AKI duration if the association was driven by general differences in surveillance. Therefore, we do not expect the associations between AKI duration and heart failure and ischemic heart disease to be solely due to differences in surveillance.

6.3.3 Confounding

Confounding refers to a distortion of the measure of effect between an exposure and an outcome and can arise in settings where exposed and unexposed patients differ with regard to covariates that affect the outcome.[173,202] An example of a confounding factor could be hypertension when examining if the duration of AKI is associated with the risk of CKD. Hypertension is a well-established risk factor for CKD and its prevalence varied across AKI duration groups in Study IV. If unaccounted for, this could lead to a biased estimation of the causal relationship between AKI duration and CKD. Therefore, confounding needs to be accounted for when examining the causal effect of an exposure on an outcome in observational studies. This can be done by design (by, e.g., restriction or matching) or in the analyses (by, e.g., standardization, stratification, or multivariable regression). Covariates for confounder adjustment were identified using a disjunctive cause criterion, i.e., pre-exposure covariates that were considered a cause of the exposure, outcome, or both.[173]

In all studies, we performed stratified analyses, e.g., by sex and age when assessing pCr testing frequencies (Study I), or by sex, age, and AKI stage when examining the exposure-outcome association (Studies II-IV). In Study III, we controlled for confounding by age and sex across regions and municipality categories by direct standardization. Moreover, to control for differences in, e.g., baseline eGFR, morbidity, and prescription drug use, we adjusted regression analyses for confounders (Studies III and IV). Nonetheless, adjusted measures of effect might still suffer from uncontrolled confounding. Uncontrolled confounding can be a consequence of residual confounding due to misclassified confounders, unmeasured confounding due to missing information, and unknown confounding from unidentified confounders. We obtained information on confounders from several registers including the DNPR, the NPR, and the laboratory databases. As discussed above, the sensitivity and specificity of diseases in the DNPR vary. Especially conditions mainly treated in primary care, such as diabetes, are at risk of being misclassified in the DNPR and adjustment for such confounders could result in residual confounding.[203] To minimize the risk of residual confounding due

to misclassification when adjusting for diabetes and kidney disease, we included information on antidiabetic treatment from the NPR and on eGFR from the laboratory databases.[204]

6.3.4 Random error

Random error pertains to the statistical precision of estimates, which is affected by random variation or chance.[173] The level of random error can be minimized by increasing the size of the study population. The use of population-based registries allowed us to identify large cohorts of patients with AKI, which enabled a high statistical precision and limited the role of random error. However, when stratifying analyses or studying rare outcomes, e.g., when examining regional variation in outpatient contact with a nephrology department after KRT-requiring AKI (Study III), the precision fell making the result more susceptible to random error.

In Studies III and IV, we evaluated random error by supplementing point estimates with a 95% CI and refrained from using statistical significance testing in agreement with current guidelines and recommendations.[173,205,206] In Study II, we examined continuous outcomes of eGFR levels and eGFR slopes and changes in these. In line with the descriptive purpose of the study and the non-normal distribution of these outcomes, we chose to present outcomes as medians with IQRs, which also illustrated the variation in outcomes within the study population.

6.3.5 Additional considerations

In Study II, we used repeated measures of pCr to determine eGFR levels and eGFR slopes, which enabled us to describe changes in eGFR from before to after AKI. We accounted for the clustering of data by performing linear regressions for each patient before and after AKI. Furthermore, the use of individual linear regressions eliminated the problem of variation in the number of pCr tests as each patient only contributed with summary statics in the form of eGFR levels, eGFR slopes, and differences in these. Finally, confounders within each subgroup were balanced at the time of AKI as the eGFR slopes and eGFR levels before and after AKI were compared on an individual-level. The application and use of this method in studies of changes in kidney function is well-established and has a close resemblance with clinical practices, where a physician evaluates a patient's change in kidney function by comparing current and prior tests.[187,207] Another method for handling clustered data is the use of random effects (mixed) models.[171,187,207] These models handle repeated measurement data by accounting for the level of clustering in the model. This method has become increasingly popular in kidney research due to advantages such as the possibility of comparing subgroups through confounder adjustment and no requirement for a specific

number of observations.[187,207] For these reasons, we also fitted a mixed model. However, we were unable to satisfy the assumption of homoscedasticity as the residuals were not constant across the range of predicted values. Therefore, we did not include the results from the mixed model in Study II. Similar concerns with mixed model assumptions in studies of kidney function have previously been expressed.[185]

If applicable, a mixed model would have allowed for the inclusion of patients with fewer pCr tests. However, it would not have eliminated selection bias. We would still only be able to include information on eGFR from patients who survived beyond 90 days after AKI onset and had one or more outpatient pCr tests. This is pivotal to ensure that only tests performed during a steady state after the transition from an acute to a chronic event are included. Advanced models capable of handling the informative censoring of death have been developed; however, as these combine random effects models with survival models, assumptions for both models would still need to be fulfilled, which hindered the application in Study II.[208]

6.3.6 Generalizability and transportability

Generalizability reflects the extent to which estimates from a study can be applied to the source population, while transportability refers to whether the estimates can be applied to an external population, e.g., patients with AKI in another country.[173] The studies included in this dissertation are all population-based cohort studies. In Study II, analyses were restricted to patients with repeated pCr tests before and after AKI. The included population was younger, more comorbid, and had a lower 1-year mortality rate than the overall cohort of patients with AKI. The inclusion of patients surviving to have repeated pCr tests following AKI means that results may not be generalizable to the overall population of patients with AKI. However, we believe that these results are generalizable to the clinically relevant cohort of patients who survive the initial event and for whom long-term changes in kidney function are of importance. Furthermore, results were robust when expanding the study population to patients with two or more pCr tests before and after AKI.

In Study IV, we included patients with AKI who had an outpatient baseline pCr test within the prior year and assessment of AKI duration within seven days following AKI onset. Characteristics of the included patients and all patients with AKI were comparable overall and we would not expect the association between AKI duration and outcomes of CVD and CKD to differ from that of patients without a pCr test within the prior year.

With the limitations above in mind, we would expect our results to be transportable to other countries with similar demographics and healthcare systems. For example, in Study III, we used the KDIGO creatinine criteria and precise estimates of population sizes and found similar rates of AKI incidence as a UK study

using similar definitions and data.[125] In addition, our findings in Study IV corroborate findings on the association between AKI duration and risks of CKD and CVD from previous smaller studies on selected patient populations.

7. Conclusions

Based on the four studies included in this dissertation, we conclude that:

1) Clinical care pCr data from the Danish laboratory databases, LABKA and the RLRR, provide long follow-up and nationwide coverage within a population-based setting making it a valuable resource for population-based studies on kidney disease epidemiology. Reflective of the clinical care setting, the pCr-tested individuals were older and more comorbid than the general population. Nonetheless, pCr testing was frequently performed in recent years with more than one-third of Danish residents having at least one test annually. The time of complete geographical coverage varied substantially between municipalities and regions. This could be of importance, e.g., if studying temporal trends in AKI and CKD and needs to be considered when designing studies based on these data.

2) AKI was consistently associated with a sustained reduction in eGFR level in patients with repeated outpatient pCr tests before and after AKI. Moreover, AKI was associated with a higher rate of eGFR decline after AKI compared with before in patients with a baseline eGFR ≥60 ml/min/1.73 m^2. These findings corroborate current guidelines recommending evaluation of kidney function after AKI. In addition, this emphasizes that the association between AKI and changes in eGFR extend beyond the immediate phase. Thus, even patients with only a minor drop in eGFR level are at risk of long-term changes in kidney function.

3) Regional differences in AKI incidence rates were minor after accounting for differences in age and sex distributions of the underlying populations. The mortality after AKI was similar across regions, while the rates of CKD and nephrology follow-up varied. The similar incidence rates of AKI found across regions in a universal healthcare system are encouraging; however, the variation in rates of CKD and nephrology follow-up after AKI warrants attention on the quality of care after AKI.

4) The duration of AKI was associated with long-term risks and rates of CKD and kidney failure. AKI duration was not associated with overall CVD. Nevertheless, there was a slight rise in rates of ischemic heart disease and heart failure with increasing AKI duration. The gradual increase in risks of CKD and kidney failure with increasing AKI duration illustrates the potential for using AKI duration as a risk marker when planning nephrology follow-up after AKI.

8. Future perspectives

Besides describing the potential of utilizing Danish pCr data for studying kidney diseases in a population-based setting, the studies in this PhD dissertation add to the knowledge on the association between AKI and changes in eGFR, regional variation in AKI incidence, prognosis and follow-up, and the association between AKI duration and prognosis.

A pivotal step in improving care for AKI is to increase clinical awareness of the condition. All health professionals should be able to recognize AKI and identify patients at increased risk of AKI. This may be aided by electronic warning systems and the use of novel biomarkers. The integration of electronic warning systems with AKI care bundles has shown promising results.[73,74] Data from the Danish registries, including the laboratory databases, could be used for validation of such warning systems in the Danish healthcare setting before implementation in the electronic health record system.

To facilitate a further understanding of the association between AKI and changes in eGFR, it would be desirable to develop consensus definitions for the evaluation of changes in eGFR. The current lack of generally agreed definitions complicates comparisons across studies and while choices for defining changes in eGFR might be arbitrary, the formulation of a common definition could stimulate the development of the field and foster redefined definitions similar to the RIFLE, AKIN, and KIDIGO definitions for AKI.

Identification of modifiable prognostic factors is essential for translating knowledge on variation in AKI incidence and prognosis into improved treatment of patients. A further examination of the causes for variation in the development of CKD following AKI across the Danish regions could address the effectiveness of introducing kidney protecting initiatives covering both primary care and hospital settings.

Further studies examining whether AKI-directed interventions, such as the AKI care bundles, can modify the occurrence of kidney and cardiovascular adverse outcomes are warranted. Similar to the recent work on the timing of KRT and the use of remote ischemic preconditioning in AKI,[209-212] interventional studies are central for understanding whether targeted treatments can limit and prevent progression of AKI duration and severity and whether this changes the prognosis.

9. Summary

Acute kidney injury (AKI) is a common and serious condition associated with increased morbidity and mortality. Thus, AKI places a substantial burden on the healthcare system, which is expected to increase in the coming decades. On this basis, this PhD dissertation examined the occurrence and prognosis of AKI in Denmark using population-based registries. We assessed the plasma creatinine (pCr) data from the regional Clinical Laboratory Information System Research Database (LABKA) and the nationwide Register of Laboratory Results for Research (RLRR) (Study I), changes in kidney function from before to after AKI (Study II), regional variation in AKI incidence and prognosis (Study III), and the association between AKI duration and chronic kidney disease (CKD) and cardiovascular disease (CVD) (Study IV).

In Study I, we found that during 1990-2018, LABKA and the RLRR included more than 61 million pCr tests from 4.6 million individuals with complete nationwide coverage from October 2015. During 2016-2018, more than one-third of Danish residents had a pCr test each year. Tested individuals were more females, older, and had more comorbidities than the general population.

In Study II, we found a drop in estimated glomerular filtration rate (eGFR) level from before to after AKI in patients with repeated outpatient pCr tests. Furthermore, AKI was associated with a higher rate of eGFR decline among patients with baseline eGFR ≥60 ml/min/1.73 m^2, while a lower rate of eGFR decline was found in patients with baseline eGFR <60 ml/min/1.73 m^2.

In Study III, we found regional variation in AKI incidence, which was, in part, explained by differences in demographics across the Danish regions. Mortality after AKI was similar; however CKD, outpatient nephrology contact, and biochemical follow-up varied across regions.

In Study IV, we found higher rates of CKD and kidney failure with increasing AKI duration. AKI duration was not associated with overall CVD, but increasing AKI duration was associated with slightly higher rates of ischemic heart disease and heart failure.

In conclusion, we showed that Danish laboratory databases hold longitudinal and nationwide pCr data making them an important source of information for studies on kidney diseases. Moreover, we found regional variation in CKD and follow-up after AKI. Finally, we showed that AKI is associated with long-term changes in eGFR and that AKI duration is associated with increased risks of CKD and subgroups of CVDs.

10. Dansk resumé

Akut nyrepåvirkning (ANP) er en hyppigt forekommende og alvorlig tilstand associeret med øget morbiditet og mortalitet. ANP udgør derfor en betydelig belastning for sundhedsvæsenet, som forventes at stige i de kommende år. På den baggrund har vi i denne ph.d.-afhandling undersøgt forekomsten af og prognosen for ANP i Danmark ved brug af populationsbaserede registre. Vi har undersøgt registreringen af plasma kreatinin (pKr) tests i det regionale laboratorieinformationssystem, LABKA, og den landsdækkende Laboratoriedatabasens Forskertabel (Studie I), ændringer i nyrefunktion fra før til efter ANP (Studie II), regional variation i ANP incidens og prognose (Studie III) og associationen mellem varigheden af ANP og kronisk nyresvigt samt hjerte-kar-sygdom (Studie IV).

I Studie I fandt vi, at LABKA og Laboratoriedatabasens Forskertabel for perioden 1990-2018 indeholder svar på mere end 61 millioner pKr-tests fra 4,6 millioner individer med komplet landsdækkende indrapportering fra oktober 2015. I 2016-2018 fik mere end en tredjedel af alle danskere foretaget en eller flere pKr-tests hvert år. De testede individer var oftere kvinder, samt ældre og mere komorbide end baggrundsbefolkningen.

I Studie II fandt vi et fald i niveauet af estimeret glomerulær filtrationshastighed (eGFR) fra før til efter ANP blandt patienter med gentagne pKr-tests fra ikke-akutte kontakter med sundhedsvæsenet. Derudover var der efter ANP et større årligt fald i eGFR for patienter med baseline eGFR ≥60 ml/min/1.73 m^2, men et mindre årligt fald i eGFR for patienter med baseline eGFR <60 ml/min/1.73 m^2 sammenlignet med før ANP.

I Studie III fandt vi regional variation i incidensen af ANP, som var delvist forklaret af forskelle i demografien på tværs af de danske regioner. Mortaliteten efter ANP var sammenlignelig, mens udvikling af kronisk nyresvigt, biokemisk opfølgning, og ambulante kontakter til nefrologiske afdelinger varierede på tværs af regioner.

I Studie IV fandt vi, at varigheden af ANP har betydning for udvikling af kronisk nyresvigt og terminal nyresvigt. Generelt set var der ikke sammenhæng mellem varigheden af ANP og udvikling af hjerte-kar-sygdom, men varigheden af ANP havde betydning for udvikling af iskæmisk hjertesygdom og hjertesvigt.

Med denne afhandling har vi vist, at danske laboratoriedatabaser indeholder pKr-data med både langvarig og landsdækkende dækning, hvilket gør dem til en værdifuld ressource for studier af nyresygdomme. Vi fandt regional variation i kronisk nyresvigt og opfølgning efter ANP. Desuden har vi vist, at ANP er associeret med varige ændringer i eGFR, og at varigheden af ANP er associeret med udvikling af kronisk nyresvigt og visse hjerte-kar-sygdomme.

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12. Appendices

The full versions of Studies I-IV are provided in the Appendices I-IV:

Study I

Appendix I

Study II

Appendix II

Study III

Appendix III

Study IV

Appendix IV