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CONSEQUENCES OF KIDNEY DYSFUNCTION IN THE COMMUNITY. HEALTH CARE-BASED EPIDEMIOLOGICAL STUDIES FROM THE STOCKHOLM CREATININE MEASUREMENTS (SCREAM) PROJECT

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my parents,
my wife
and my daughters

POPULAR SCIENCE SUMMARY OF THE THESIS

Chronic kidney disease (CKD) is a global health problem that is becoming more common in all parts of the world. CKD often does not give rise to symptoms, and might therefore pass undetected by the individual, but increases the risk of several other serious health concerns, such as cardiovascular disease. CKD can be diagnosed, and staged, through common laboratory tests. However, CKD has been under-reported in routine medical care, creating difficulties in establishing just how common this condition is in the general population. Furthermore, the consequences of CKD in many areas of health care have not been sufficiently studied.

This thesis is built on a health care extraction consisting of laboratory and other health care information from 1,1 million individuals residing in Stockholm County in the years 2006 to 2011. We called it the Stockholm CREAtinine Measurements Project (SCREAM). Thanks to the unique personal identification number, information from laboratories could be linked to various health care registries; thereafter all data was anonymized.

The aim of the thesis was to describe the creation of SCREAM, and to explore the impact of CKD in health aspects where it has previously not been sufficiently evaluated. In all the following studies, the study participants were selected from the SCREAM population.

In **paper I**, we investigated the representativeness and regional coverage of SCREAM, and found that it covered a large portion of the Stockholm population overall, and that coverage was particularly high in population segments that are at greater risk of CKD, namely the elderly and those with other chronic diseases, such as diabetes and ischemic heart disease (98% and 97%, respectively, of people with these diagnoses were included in SCREAM).

It is well known from previous studies that CKD confers a higher risk of death, but little has been written on the causes of death among persons with CKD. Knowing the causes, we thought, might clarify the need for preventive measures. Therefore, in **paper II**, we sought to understand how causes of death correlate with kidney function late in life. We saw that with lower kidney function estimates, cardiovascular disease, especially heart failure, infections and diabetic complications were more frequently the ascribed cause of death.

Paper III examines how kidney function affects the risk of fractures among persons with CKD, and to what extent the occurrence of a fracture influences the risk of subsequent major adverse cardiovascular events (MACE) - such as cardiac infarction or stroke - or death. It demonstrates a gradually increasing risk for fractures with decreasing kidney function, and a manifest

increase in the risk of MACE in the aftermath (both short and long term) of either a hip or non-hip fracture.

Paper IV, finally, is an inquiry into the association between kidney function and the risk of hypoglycaemia (a low blood sugar that poses a threat to the health of the individual) in people with diabetes. The study shows a consistently higher risk of hypoglycaemia with lower kidney function.

ABSTRACT

Chronic kidney disease (CKD) is affecting an increasing share of the world's population, and presents a global health problem. The prevalence of CKD in society and its implication for various health outcomes have been difficult to assess due to unawareness and underuse of clinical diagnoses for CKD in clinical practice. The present work aims to inform the reader of the epidemic of CKD in Sweden through a newly created repository of health care data.

Paper I describes the creation of the Stockholm CREAtinine Measurements (SCREAM) project, a health care extraction containing all creatinine values collected between 2006 and 2011 in the Stockholm region, together with a host of associated laboratory data, dispensed prescriptions, and diagnostic and demographic information. SCREAM has a good representation of the general population of Stockholm county, particularly of the elderly, with a coverage exceeding 90% among persons aged 65 or above. The coverage of people with diabetes was 98%, and that of ischemic heart disease was 97%. SCREAM captured 89% of deaths occurring in the region those years.

Paper II investigates how causes of death correlate with estimated glomerular filtration rate (eGFR) in the last year of life. We observed a higher proportion of death from cardiovascular disease and infections with lower eGFR. Among cardiovascular causes, heart failure and arrhythmias became more common with lower eGFR. Diabetes complications were also more common in lower kidney function strata.

Paper III evaluates the association between kidney function and the risk of incident fractures among people with CKD stages 3-5 (not on dialysis), and whether developing a fracture predicts subsequent risk of death or major cardiovascular adverse events (MACE). We found a gradual increase in the risk of fractures with lower eGFR in persons with CKD 3b-5 (HR 2.47 (1.94- 3.15) for hip fractures and 1.50 (1.25- 1.80) for non-hip fractures, in CKD 5 vs CKD 3a). In the aftermath of a fracture, mortality and MACE incidence were considerably increased, in both short (<90 days) and long term (>= 90 days) follow-up, as compared to non-fracture periods.

Paper IV investigates the risk and severity of hypoglycaemia in relation to kidney function, among people with diabetes followed in outpatient care. We observed a significant, gradual rise in the multivariable-adjusted risk of hypoglycaemia with lower eGFR. Several other risk factors for hypoglycaemia were identified, among them type 1 diabetes, presence of diabetic complications, and liver diseases. The risk of fatal hypoglycaemia was also higher with lower eGFR.

LIST OF SCIENTIFIC PAPERS

I. **Runesson B**, Gasparini A, Qureshi AR, Norin O, Evans M, Bárány P, Wettermark B, Elinder CG, Carrero JJ. The Stockholm CREAtinine Measurements (SCREAM) project: protocol overview and regional representativeness. Clinical Kidney Journal, 2016 Feb; 9(1): 119-27.

II. **Runesson B**, Qureshi AR, Gasparini A, Lindholm B, Bárány P, Elinder CG, Carrero JJ. Causes of death across categories of estimated glomerular filtration rate: The Stockholm CREAtinine Measurements (SCREAM) project. PLoS One, 2019 Jan 16;14(1).

III. **Runesson B**, Trevisan M, Iseri K, Bárány P, Lindholm B, Qureshi AR, Elinder CG, Carrero JJ. Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine measurements project. Nephrol Dial Transplant. 2020 Nov 1;35(11):1908-1915.

IV. **Runesson B**, Xu Y, Qureshi AR, Lindholm B, Bárány P, Elinder CG, Carrero JJ. Association between reduced kidney function and incident hypoglycaemia in people with diabetes: The Stockholm Creatinine Measurements (SCREAM) project. Diabetes Obes Metab. 2020 Aug;22(8):1425-1435.

CONTENTS

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body mass index
BMD	Bone mineral density
C-G	Cockcroft-Gault
CGM	Continuous glucose measurement
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CKD-MBD	Chronic kidney disease – mineral bone disorder
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
DPP-4	Dipeptidyl peptidase-4
FGF 23	Fibroblast growth factor 23
FRAX	Fracture risk assessment tool
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide 1
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
PTH	Parathyroid hormone
RRT	Renal replacement therapy
SCREAM	Stockholm creatinine measurements project
SGLT-2	Sodium-glucose co-transporter-2
UACR	Urinary albumin to creatinine ratio

INTRODUCTION

This work evaluates some aspects of chronic kidney disease (CKD) in a Stockholm representative population accessing healthcare. The thesis deals with under-recognized complications of CKD, such as bone fractures and diabetes-related hypoglycaemia, which will serve as examples of the risk modifying effect of kidney dysfunction in two medical areas with public health implications.

1.1 Chronic kidney disease.

1.1.1 Definition, assessment, staging

Chronic kidney disease (CKD), as defined by the Kidney Disease Improving Global Outcomes (KDIGO) initiative, is an abnormality of kidney structure or function, with implications for the health of the individual, persisting for more than three months [1]. The initial insult varies, as do progression rate and prognosis, but the chain of events that unfold in response to a decreasing number of functioning nephrons is similar across a wide range of conditions, resulting, if uninhibited, in a state of fibrosis (termed glomerulosclerosis when affecting the glomeruli) [2]. Renal deterioration may occur precipitously (as in severe inflammatory glomerular diseases or in total mechanical obstruction), or may develop surreptitiously, escaping clinical attention until advanced and often irreversible disease has been established. CKD is staged according to estimated glomerular filtration rate (eGFR) and amount of albumin leakage in the urine (albuminuria). GFR is an expression of the amount of plasma that is filtered over the glomerular capillaries per unit of time [3]. It is not readily measured, but can be estimated from the clearance of an exogenous marker, such as iohexol, or, which is much more common in clinical practice, from steady state plasma levels of endogenous markers, such as creatinine or cystatin-C. There are several equations for GFR estimations from endogenous markers, the currently most widely used being the creatinine-based Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) formula, which takes into consideration serum creatinine (on a logarithmic scale), sex, ethnicity (black/non-black) and age (on a natural scale) [4]. Since GFR depends on body mass, eGFR is indexed to an average body surface area [3]. Albuminuria alone can signify CKD, and is an independent marker of severity and prognosis [5]. A correct staging of CKD therefore includes both eGFR and albuminuria levels, according to KDIGO guidelines [1]. However, the latter is not as yet routinely used in clinical practice, possibly from underrecongition of its clinical implications. Creatinine-based eGFR is the most widely used indicator of kidney function. When CKD is defined solely by eGFR, two

consecutive estimates, with at least three months apart, of less than 60 ml/min/1.73 m² are considered indicative of CKD [1].

Table 1. CKD staging according to glomerular filtration rate and albuminuria

Glomerular filtration rate		**Comment**	**Albuminuria category**		
			A1 (UACR <30)	A2 (UACR 30-300)	A3 (UACR >300)
G1	>90 ml/min/1.73 m^2	*Normal or elevated*	*can be part of normal ageing*	*Indicative of CKD*	*Indicative of CKD*
G2	60-89 ml/min/1.73 m^2	*Mild decrease (can be part of normal ageing)*	*can be part of normal ageing*		
G3a	45-59 ml/min/1.73 m^2	*Indicative of CKD*			
G3b	30-44 ml/min/1.73 m^2	*Indicative of CKD*			
G4	15-30 ml/min/1.73 m^2	*Severely decreased*			
G5	<15 ml/min/1.73 m^2	*End-stage renal disease*			

UACR, urinary albumin to creatinine ratio (mg/g).

Adapted from Kidney Disease: Improving Global Outcomes CKD Work Group (2012) [1].

There is an ongoing debate on whether the threshold for CKD should be modified by age, since a certain loss of kidney function is part of healthy ageing [6]. Although age is considered in the CKD-EPI formula, the presence of low eGFR among the elderly might theoretically not be indicative of true CKD, and the prognostic relevance of reduced eGFR corresponding to CKD 3A among elderly subjects has been questioned [7]. Nonetheless, CKD 3B (eGFR<45 ml/min), or a faster than average eGFR decline is associated with the presence of cardiovascular and metabolic comorbidities, also in the elderly [6-8]. The CKD-EPI formula has been shown to give higher estimates of GFR in individuals above 70 years than both iohexol clearance and alternative eGFR formulas [7, 8].

1.1.2 Clinical implications of CKD

Diabetes and hypertension are the dominant contributing causes of CKD in most regions of the world [9, 10], but the spectrum of causes of CKD is wide, including infectious and autoimmune diseases, congenital anomalies, medication toxicity, diseases of the urinary tract, and a variety of single-gene disorders [11]. Early detection of CKD is important, as it enables prevention of progression and mitigation of adverse outcomes (table 2). Progression of CKD from moderate to severe stages is strongly influenced by the competing risk of death, which explains the large overrepresentation of earlier stages of CKD (vis-à-vis more advanced forms) in the general population, and which underlines the need for preventive measures [12].

Table 2. Examples of clinical consequences of CKD

Clinical area	Consequences
Electrolyte disturbances	Hypertension, alterations in volume status (through dysnatremia), arrhythmia (from hyperkalemia)
Cardiovascular disease	Two-to-three-fold increase in cardiovascular mortality in CKD stages three to four [13, 14].
Anaemia	Reduced quality of life, increased CVD risk and mortality [15]
Mineral and bone disorders	Fragility fractures, vascular stiffness, cardiomyopathy [16].
Adverse drug reactions	Risk of drug accumulation and unwarranted effects because of altered drug metabolism and polypharmacy [17].
Metabolic acidosis	Muscle wasting, CKD progression, bone demineralization [18].
Malnutrition, protein hypercatabolism	Increased morbidity, mortality and CKD progression [19].
Miscellaneous	Increased risk of infections [20], depression [21], hypercoagulability and altered haemostasis [22].

CVD, cardiovascular disease

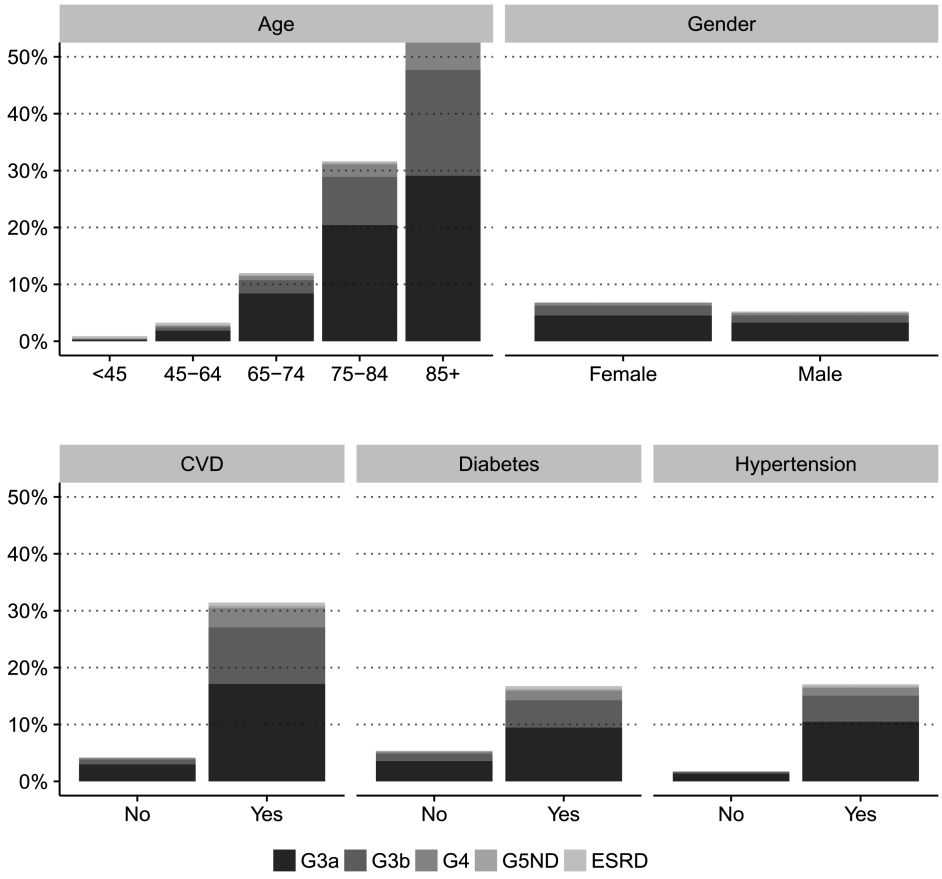
Efforts to minimize CKD progression and its side effects consist of dietary, life-style and pharmacological interventions. Studies in primary care, however, where most persons with kidney dysfunction are surveyed, have shown such measures to be under-utilized, in part because of lack of CKD awareness, or difficulties in implementing treatment according to guidelines in these patients [23-25].

2 BACKGROUND

2.1 Estimations of CKD prevalence

CKD has emerged as a global health problem of increasing prevalence, complication rates and health care costs, in affluent and emerging economies alike, paralleling an ageing global population [9, 10, 26, 27]. CKD has been estimated to affect 9-15% of the population, both in developed countries and globally [9, 10, 28-32]. According to the Global Burden of Disease Study, global prevalence of CKD rose by 29% between 1990 and 2017 [10]. Prevalence assessments vary widely, possibly reflecting heterogeneity of methods and non-response bias, but also for reasons of regional differences, demographic composition (with older populations harbouring a larger CKD group) or for lack of effective surveillance in some countries [12, 27, 33, 34]. For example, variation was substantial among European countries in an analysis of aggregated survey data: from 3% in Norway to 17% in Northeast Germany for CKD of any stage, and from 1% to 6% for CKD stages 3-5 in Italy and Germany, respectively [35]. CKD prevalence also varies with age and co-morbid conditions (**figure 1**).

Figure 1. CKD prevalence in relation to age and co-morbidities



From Gasparini et al. 2016 [36], reprinted with permission. Data for these estimates were collected from the SCREAM cohort described below.

Most people are unaware of their disease [36-39], partly because symptoms of CKD appear at late stages, and because there are no effective screening programs. Clinicians underutilize diagnostic codes of chronic kidney disease [36, 40, 41] and this limits the capacity of administrative registers to inform epidemiological studies on this condition. When I started my PhD project, there was no reliable information on the prevalence of CKD in Sweden, neither was there any population material to study the consequences of CKD and kidney function decline in the general population. We saw an opportunity in the fact that plasma creatinine is a commonly measured biomarker in healthcare, based on which we could make estimations of kidney function in the population. This was the background for the SCREAM project whose creation I describe in PAPER I.

2.2 CKD and causes of death

According to the Global Burden of Disease consortium, deaths ascribed to CKD have increased by 41.5 % between 1990 and 2017, making it the 12th foremost cause of death in that year [10]. This growth is attributed to increasing rates of non-communicable diseases, greater CKD awareness and, not least, ageing populations. Testimony to the latter is that the age-adjusted CKD mortality remained constant during the same period (in contradistinction to CVD and cancer age-adjusted mortality which declined) [10].

Both reduced eGFR and the presence of albuminuria are associated with mortality in the general population [14, 42-44]. Cardiovascular disease is probably the most prominent complication and cause of death among patients with CKD, partly because of risk factors common to both conditions, such as arteriosclerosis, hypertension, diabetes and the metabolic syndrome, and partly because of traits that are inherent to the CKD phenotype, such as low grade inflammation, vascular calcification and an atherogenic lipid profile [13, 45]. Independent of traditional cardiovascular risk factors, albuminuria or low eGFR increase CVD risk [46-48]. In patients with diabetes or hypertension, the presence of CKD also magnifies the risk of cardiovascular events [10, 47], and among European patients initiating dialysis, CVD attributed mortality was 8.8 times higher than in the general population [49]. However, non-cardiovascular causes of death are almost equally elevated in these patients [49] but receive less attention. The relative importance of non-CVD mortality in patients with end-stage renal disease (ESRD) was also underlined by another European cohort study of incident dialysis patients, where 41% and 49% of deaths were of CVD and non-CVD origin, respectively [50]. As an example of non-CVD causes, death from sepsis has been reported at a 50-fold higher incidence among US patients with ESRD than in the general population [51], and a higher risk of severe infection has been described also among people with non-dialysis CKD [52]. In a US health care registry of 38,520 patients with CKD, there was an increased all-cause mortality for every stage of worsened eGFR or UACR, with an equal contribution from CVD and non-CVD/non-malignancy causes [42]. In a Korean registry of private health care seekers, an increased mortality was seen in people with eGFR<45 ml/min/1.73 m^2, that was mainly ascribed to non-CVD/non-cancer diseases [43].

Few reports have comprehensibly evaluated causes of death of patients with CKD. A study of deceased people in Alberta, Canada, showed that deaths due to cardiovascular disease and infections were more common in patients with an eGFR <60 ml/min/1.73 m^2, and death attributed to malignant diseases less prevalent [53].

Characterizing the causes of death in relation to kidney function might bring complementary information of value for health care planning and implementation of cause-specific prevention measures. Against this background, we decided in PAPER II to evaluate the reported causes of death for patients with different stages of CKD in our region.

2.3 Fracture risk and consequences of fractures in CKD

2.3.1 Characteristics of CKD-MBD

The term chronic kidney disease - mineral bone disorder (CKD-MBD) applies to a clinical spectrum of derangements in bone turnover, mineralization and growth, with ensuing extra-skeletal calcification [16]. The landmarks of CKD-MBD are phosphate retention, calcium imbalance, 1,25-dihydroxyvitamin D (1,25 D) deficiency and elevated parathyroid hormone (PTH) levels [54]. As the number of functioning nephrons declines in the course of CKD, a complex series of hormonal responses sets in, to maintain a narrow physiologic range of ionic calcium and phosphate [54]. The main actors are parathyroid hormone (PTH), circulatory fibroblast growth factor 23 (FGF-23) and Klotho, which acts both on renal tubuli (facilitating phosphaturia), and systemically, as the main regulator of key hormones of the calcium-phosphate homeostasis [55]. These compensatory measures may, however, prove insufficient and even detrimental, as CKD progresses, and serum levels of Klotho drop, provoking a surge in FGF-23 and PTH that leads to cardiac hypertrophy, vascular calcification and arterial stiffness [56]. Simultaneously, phosphate retention stimulates PTH synthesis, creating a secondary hyperparathyroidism that accelerates bone turnover and heightens the risk of fragility fractures [57]. Hyperphosphatemia, which develops alongside growing tubular resistance to the phosphaturic effects of PTH, has several harmful effects on bone and vascular health, for instance by inhibiting hormonally active (1,25-(OH)2-D3) vitamin D generation, and by triggering smooth muscle cell calcification in the vascular wall [56, 58]. Hence, a pathological skeletal and cardiovascular phenotype develops, in which increasing arterial calcification parallels a loss of bone density [59].

CKD-MBD and osteoporosis are partially overlapping entities. Osteoporosis is defined as a reduced bone strength that leads to an increased risk of fractures, or a *T* score ≤ -2.5 [60, 61],. In CKD-MBD, bone strength may be compromised from either reduced mineral density or aberrant bone quality [62]. Unsurprisingly, osteoporosis and CKD often co-exist, and CKD-associated osteoporosis can be assessed through a bone mineral density (BMD) measurement in patients with CKD [61]. Established risk factors for osteoporotic fractures are low peak bone

mass, female sex, age, low BMI, hyperthyroidism, prior fractures, malabsorption, inflammatory bowel disease, glucocorticoid use and vitamin D deficiency [63]. The surplus risk conferred by CKD is insufficiently investigated.

2.3.2 Fracture risk in CKD

An increased risk of fractures has been demonstrated in haemodialysis populations [64-66] and among kidney transplant recipients [65, 67]. For patients with CKD not under renal replacement therapy (RRT), evidence of an increased fracture risk is less clear, with excess risk of fractures found in some studies [68-75], but in others not [76, 77]. Most previous studies have focused on hip fractures only, some on one sex only [70, 71, 76]; some have excluded pathological fractures [73] (which risks excluding CKD-associated osteoporotic fractures); most studies rely on single, unconfirmed GFR estimates, some have few participants with CKD [69, 75], or suffer from the possibility of reversed causation [68, 73] (**table 3**).

Table 3. Studies on fracture risk in chronic kidney disease

Author (year)	**Nickolas (2006) [68]**	**Fried (2007) [69]**	**Ensrud (2007) [76]**	**Dooley (2008) [70]**	**Lacroix (2008) [71]**	**Elliot (2013) [77]**	**Naylor (2014) [72]**	**Kim (2016) [73]**	**Robertson (2018) [74]**	**Chen (2018) [75]**
Study population	NHANES III particpiants with data on eGFR and hip fracture history (n=6,270)	The Cardiovascular Health Study Cohort (n=4,699)	The Study of Osteoporotic Fractures Cohort (n=969; 299 cases)	Male patients at Veterans Affair Medical centers (n=33,091)	Women's Health Initiative Observational Study (n=794; 397 cases)	Population-based cohort, Alberta, Canada (n=1,815,943	Health care databases, Ontario, Canada (n=679,114)	US National inpatient sample (n=278,018)	Regional health care user cohort, Scotland (39,630)	Longitudinal Aging Study Amsterdam (n=1,477)
Study design	Cross-sectional	Retrospective cohort study	Case-control	Retrospective cohort	Case-control	Retrospective cohort	Retrospective cohort	Cross-sectional	Retrospective cohort	Prospective cohort

Author (year) – *cont.*	**Nickolas (2006) [68]**	**Fried (2007) [69]**	**Ensrud (2007) [76]**	**Dooley (2008) [70]**	**Lacroix (2008) [71]**	**Elliot (2013) [77]**	**Naylor (2014) [72]**	**Kim (2016) [73]**	**Robertson (2018) [74]**	**Chen (2018) [75]**
Main finding	CKD associates with prevalent hip fractures	Increased risk of hip fracture in women but not men with CKD	Increased risk of hip, not vertebral fractures with reduced eGFR.	Increased risk of hip fractures in CKD 4 as compared to eGFR> 60 ml/min/1.73 m^2.	OR hip fracture 2.50 (1.32–4.72) in eGFR< 60 ml/min/1.73 m^2	No significant association btw eGFR and fractures (hip, wrist, vertebrae).	Graded increase in fracture risk with lower eGFR.	Fracture risk and fatality associated with CKD	Increased risk of hip fractures in CKD 3 and 4 but not in CKD 5.	Increased risk of fractures in eGFR <57 ml/min (HR 1.36; 95% CI 1.15–1.60).
Limitations	Causal inference hindered by cross-sectional design	Actively recruited participants, exposure and covariates assessed only at baseline.	Women only. Significant results only by C-G, not MDRD equation.	Male health care seeking veterans only.	Only women. eGFR assessed only at baseline (mean 7 years before outcome)	Single eGFR, at baseline.	No adjustments for co-morbidities and medication.	Risk of reversed causation. Relying on ICD codes for CKD.	Low number of events. Comorbidities assessed by in-hospital records only.	Self-reported outcome and comorbidities, single eGFR.

NHANES III, Third National Health and Nutrition Survey. C-G, Cockcroft-Gault, MDRD, Modification of Diet in Renal Disease

Considering the conflicting evidence, we thought it would be valuable to ascertain the risk of fractures in a large cohort of CKD patients from a population representative sample with extensive clinical information available. We hypothesized that the risk of fractures would increase with lower kidney function.

2.3.3 Major clinical consequences of fractures in CKD

In the general population, hip fractures augment mortality, both in the short and long term [78, 79]. Likewise, in patients on haemodialysis, a 2-fold mortality rate following incident hip fractures has been described [80, 81]. Moreover, general population studies indicate an increased risk of ischemic heart disease in people that have suffered a hip fracture [82], and men and women with prior fragility fractures, osteoporosis, or a low BMD [83-85].

However, mortality and other health sequelae of fractures in persons with non-dialysis requiring CKD have been less studied. CKD has been associated with an increased in-hospital mortality following hip fractures [73]. Reduced eGFR at admission for hip fracture has also been positively correlated to short term [86] and one-year mortality [87, 88], but these analyses cannot separate true CKD from an acute eGFR reduction related to severe injury. In a Scottish health care extraction with 915 identified hip fractures, patients with CKD 4 had a higher mortality (rate ratio 2.04, 95% CI 1.44 to 2.89) than those with normal kidney function [74].

At the time we were designing PAPER III, there were, to the best of our knowledge, no studies evaluating the possibly increased cardiovascular risk following incident fractures in patients with CKD. We thought it would be of importance to quantify the occurrence and timing of adverse cardiovascular events in patients with CKD who had suffered a fracture.

2.4 CKD, diabetes and hypoglycaemia risk

2.4.1 Clinical aspects of hypoglycaemia in CKD

CKD and diabetes are intertwined conditions, that both make up considerable challenges to public health. CKD and type 2 diabetes share several risk factors [89, 90] and largely affect the same populations. The global adult prevalence of diabetes was estimated at 9.3% in 2019 [91].

More specifically, diabetes was present in 40% of persons initiating RRT in Sweden in 2017, and one fourth of incident RRT patients had diabetic nephropathy as main etiological cause (Swedish Renal Register 2018 report, www.snronline.se). *Vice versa*, prevalence of CKD in persons with diabetes has been reported at 20-40% [92, 93].

Hypoglycaemia is defined as a low and potentially harmful level of blood sugar, according to the American Diabetes Association (ADA). It is commonly staged in three levels of severity, following ADA guidelines [94] (**table 4**). It is a common complication to diabetes treatment, often clinically silent, but sometimes presenting as dizziness, seizures or coma, risking, at worst, the patient's life [95, 96]. On top of immediate adversity, hypoglycaemia has been associated with diabetic complications [97], cardiovascular events and death in people with type 2 diabetes [98-101]. This might be explained by an increased risk of ventricular arrhythmias [102] and coronary ischemia [103], or by underlying frailty predisposing to both conditions [98, 104]. Hypoglycaemia is one of the most common, and most rapidly growing hospital-demanding adverse drug reactions in the US [105].

Table 4. Classification of hypoglycaemia.

Level one	Glucose 3.0-3.9 mmol/l.
Level two	Glucose <3.0 mmol/l.
Level three	Hypoglycaemia requiring assistance because of altered mental status

General risk factors for severe hypoglycaemia in type 2 diabetes are diabetes duration, previous diabetic complications, including hospital-encounters for hypoglycaemia, use of insulin and sulfonyl-urea, a low BMI, cognitive function decline, use of several anti-hyperglycaemic drugs, multi-morbidity and smoking [95, 100, 106, 107]. Life-style factors, such as delayed or skipped meals, strenuous exercise, stress, medication mismanagement, and carbohydrate reduction also affect hypoglycaemia risk [95].

Advanced CKD, particularly ESRD, is postulated to heighten a person's susceptibility to hypoglycaemia. Reasons include a downgraded renal gluconeogenesis, reduced insulin

clearance, a prolonged half-life of some glucose-lowering drugs, and contraindications to others, restricting therapeutic choices to insulin-based regimens [108-112]. In ESRD, malnourishment and cachexia may further increase the risk of hypoglycaemia [109].

2.4.2 Epidemiology of hypoglycaemia in CKD

In line with the disrupted glucose homeostasis described in ESRD, hypoglycaemia incidence is high in studies of haemodialysis patients [113-115]. As for the association of kidney function and hypoglycaemia incidence in the general population, epidemiological evidence is scarce, and conflicting (table 5).

Table 5. Studies on hypoglycaemia incidence in relation to kidney function

Author (year)	**Study Population**	**Study Design**	**Outcome**	**Main finding**
Moen (2009) [116]	US veterans recently hospitalized (n=243,222)	Retrospective cohort study	Blood glucose < 69 mg/dl (3.83 mmol/L).	Increased risk of hypoglycaemia in patients with eGFR <60 ml/min/1.73 m^2
Hodge (2017) [117]	Health care users >65 years, Canada (n=530,987)	Retrospective cohort study	Hospital-requiring hypoglycaemia.	Increased risk of severe hypoglycaemia with reduced kidney function
Ahmad (2019) [118]	Persons with type 2 diabetes (n=105)	Prospective cohort study	Hypoglycaemia detected by CGM	No relationship between CKD and hypoglycaemia.

CGM, continuous glucose monitoring.

These studies vary in outcome and study populations. First, Moen et al. noted a higher incidence of hypoglycaemia during one year of follow-up in US veterans (with and without diabetes) with a recent acute hospitalization, and with an eGFR below 60 ml/min/1.73 m^2. Adjustments were made for demographics and comorbidities but not for medication. As the study relied on a single eGFR, based on the creatinine closest to the index hospitalization, it was at risk for confounding by indication (because acute illness might influence both the exposure (eGFR) and the outcome, hypoglycaemia). Furthermore, more than 95% of study participants were men, which limits generalizability.

Secondly, Hodge et al. showed a gradual increase in the incidence rates of hypoglycaemia with both lower eGFR or higher albuminuria, irrespective of the use or non-use of anti-hyperglycaemic medications. They did not, however, discriminate amongst different anti-hyperglycaemic agents [117]. Besides, it would be interesting to see how their observations hold for less severe hypoglycaemia.

Finally, Ahmad et al. conducted a prospective observational study of persons with type 2 diabetes treated with insulin or sulfonyl-urea, using continuous glucose monitoring (GCM) for two six-day periods [118]. Of 105 participants, 81 had CKD. Participants from another GCM study, with eGFR >60 ml/min/1.73 m^2, were used as controls. The presence of CKD did not alter the frequency of hypoglycaemia. It is possible that the active recruitment of study participants induced a selection bias, favouring participation by people that are more engaged in their diabetes. Co-variates, including medication and medical history, were self-reported and therefore possibly less reliable. Besides, there were significant differences in baseline characteristics between CKD participants and the external controls, for example regarding diabetes duration and length of insulin use.

Tight glycaemic control in insulin treated patients with diabetes and additional CVD risk factors have failed to show significant benefits on cardiovascular outcomes and mortality in two large trials comparing different HbA1c treatment targets, but have been associated with a higher risk of severe hypoglycaemia [119-122], and possibly higher mortality [121]. These trials did not explore the influence of baseline kidney function on these outcomes or on the risk of adverse events.

Following these trials, treatment of type 2 diabetes has shifted from strict glycaemic control towards more individualized glycaemic targets [123]. In this context, and particularly in consideration of the conflicting evidence of hypoglycaemia risk in CKD, we thought it of value

to further explore the association between reduced kidney function and hypoglycaemia risk in patients with diabetes in routine clinical care, and to evaluate whether kidney function is linked to the occurrence of hypoglycaemia followed by death.

3 AIM

In this thesis, we aimed to create a register-based study cohort enriched with laboratory data, enabling evaluation of the epidemiology, management and consequences of kidney dysfunction.

Within this cohort, our specific aims were:

1. To evaluate the representativeness of our cohort against the complete population of Stockholm.
2. To assess patterns of causes of death across stages of CKD.
3. To study the association between eGFR and the risk of fractures in adults with CKD, and to describe adverse health sequelae of incident fractures in this population.
4. To explore the association between eGFR and risk of hypoglycemia in adults with diabetes.

4 MATERIAL AND METHODS

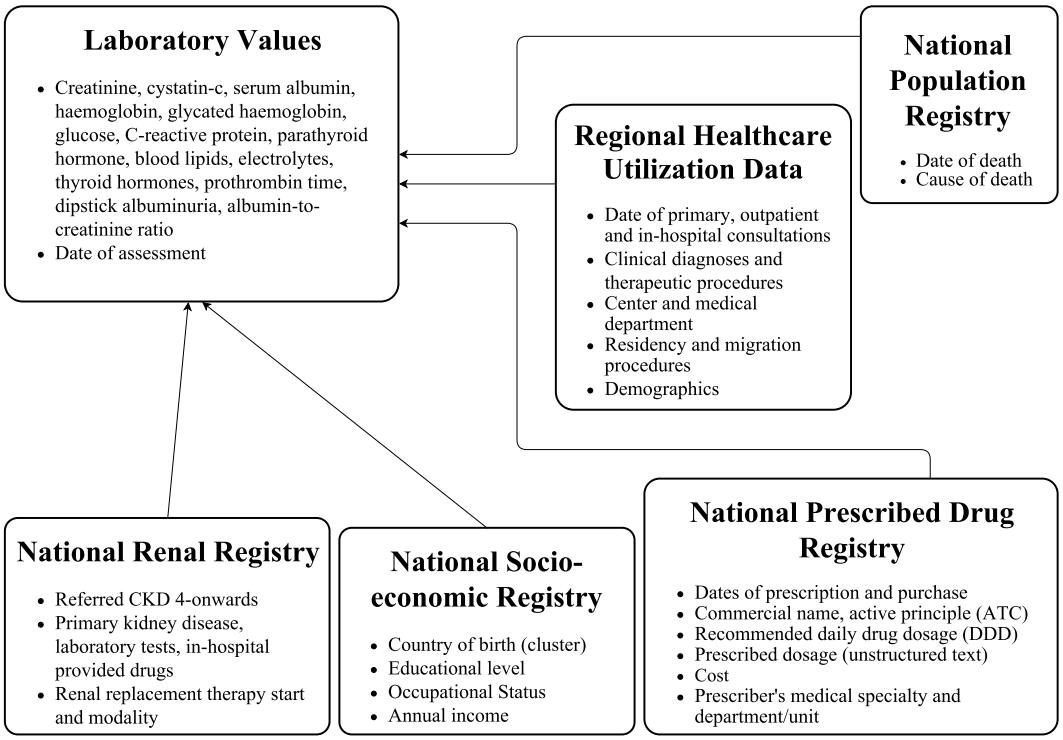
4.1 The SCREAM cohort

All the studies in this thesis are based on the the Stockholm CREAtinine Measurements project. SCREAM is a repository of laboratory data from the three major laboratory companies of the region of Stockholm (Aleris, Unilabs and Karolinska), who perform most (>93%) of laboratory tests in our region. SCREAM includes residents of Stockholm county with a valid personal identifying number, who undertook one or more serum or plasma creatinine measurement in connection with a health care encounter during 2006-2011. All creatinine values were traceable to isotope dilution mass spectroscopy standards. eGFR was estimated using the CKD Epidemiology Collaboration formula [4]. For each participant, other relevant laboratory data were retrieved.

Laboratory values were linked, via each patient's personal identification number, to healthcare utilization data retrieved from the Stockholm regional healthcare data warehouse (Vårdanalysdatabasen, VAL), including medical consultations and hospitalizations, with their respective ICD-10 codes, from primary and secondary care, from public and private health care providers [124] (**figure 1**). The National Board of Health and Welfare provided linkage of these data to the following quality registers of national coverage: The Swedish Prescribed Drug Registry (containing all pharmacy dispensations of prescribed drugs, including prescriber

specific information) [125], The Swedish Population Registry (monthly updated vital status and, when applicable, reported cause of death), and The Swedish Renal Registry, with clinical information on nephrology-referred patients, including primary kidney disease, provision of in-hospital drugs, selected laboratory values, and, when relevant, details on renal replacement therapy [126]. The personal identification number was thereafter substituted by a random identifier by Socialtyrelsen, and de-identified data was made available to the researchers.

Figure 2. SCREAM data sources.



From Runesson et al, Clin Kidney J. (2016) [127], reprinted with permission.

4.1.1 Assessment of the representativeness and regional coverage of the SCREAM cohort (paper 1)

For assessment of the cohorts' population coverage, SCREAM was compared with the complete adult population of Stockholm registered in VAL during the same period (2006-2011). Age was defined as of January 1st, 2006 for both cohorts, and representativeness was evaluated per municipality, per age strata and as per the two main diseases associated with

CKD: cardiovascular disease and diabetes mellitus. Finally, we felt it important to evaluate the proportion of deaths covered in our cohort.

4.1.2 Causes of death and kidney function (paper 2)

Population. Included in this study were all persons who passed away in the Stockholm region in the period January 1st, 2006 to March 31st, 2012, and had an outpatient eGFR assessment in the last year of life (and hence taken up in the SCREAM cohort). The last creatinine available was used as index creatinine, at which time point all other covariates (including ICD-10 codes of diagnosis pertaining to the Charlson co-morbidity score) were retrieved.

Design, exposure and outcome. This was a cross-sectional study, investigating the association between kidney function and cause of death. The exposure was outpatient eGFR in the last year of life, and the outcome was the primary cause of death, as stated in Swedish Population Register.

Statistical analyses. X^2–squared and Kruskal-Wallis tests were used to explore between-group differences. Multinomial logistic regression was used to evaluate the differences in causes of death across eGFR strata. To evaluate the possible bias of end-of life illness impacting on the index creatinine (reverse causation bias), we performed a sensitivity analysis that excluded eGFR values from the last three months of life.

4.1.3 The risk of fractures and their sequelae in adults with CKD (paper 3)

Population. The study population consisted of adults within the SCREAM cohort who had a persistently reduced eGFR, defined as two consecutive values <60 ml/min/1.73 m^2 3-12 months apart, thereby meeting the KDIGO definition of CKD . The second of these creatinine measurements defined the study baseline and the participant's eGFR. Exclusion criteria were diagnostic codes of fractures in the preceding five years, and renal replacement therapy.

Design, exposure and outcome. This was an observational study, investigating, first, the risk of fracture among patients with CKD, and, second, the consequences of incident fractures in terms of cardiovascular event risk and death. For the first part of the analysis, the exposure was eGFR, and the outcome was the occurrence of any fracture, ascertained through relevant ICD-10 codes. We excluded fractures of the face and skull because we viewed them as more likely to result from violent trauma, and to a lesser extent related to impaired bone health. Fractures

were further stratified by location (hip and non-hip). Patients were followed until the first occurrence of a fracture, end of follow-up, emigration, RRT initiation, or death. For the second part of the study, the exposure was incident fractures, and the outcomes were major adverse cardiovascular events – including ischemic heart disease, heart failure, ischemic stroke, or death from a cardiovascular cause – and all-cause death..

Statistical analyses. The risk of fractures was estimated using Cox proportional hazards' model, in which all eGFR measurements that occurred after index were considered (i.e. eGFR was a time-varying exposure), and all the co-variates in the model were updated at each new eGFR. This was done to minimize misclassification bias, as it evaluates the short-term risk of fracture with the closest eGFR to the event. Restricted cubic splines were used for assessing the non-linear association between eGFR and fracture incidence. In the second part of the study, incident fractures were considered a time-dependent exposure. In this way, every individual contributed to the fracture-free time until the occurrence of a fracture or a censoring event, and then, when applicable, to the fracture-exposed time pool. All co-variates were updated at the time a fracture occurred. Hazard ratios for MACE and death in fracture-exposed vs fracture-free time periods were calculated with Cox proportional hazards' model. We described long term and short term consequences of fractures, separating post fracture follow-up time in two intervals, <90 days and ≥90 days. To evaluate residual confounding bias, we studied diverticulitis (whose occurrence was not expected to be influenced by the development of a fracture) as a negative control outcome.

4.1.4 Risk of hypoglycemia among persons with diabetes and CKD (paper 4)

Population. The study population consisted of adults with a diagnosis of diabetes (type 1 or 2), with a newly dispensed prescription of anti-diabetic medication, and with a recent outpatient creatinine measurement to estimate their kidney function. The date of the creatinine measurement defined the baseline of the study. Study patients also needed to have at least one glucose measurement in the previous twelve months, to ensure that we selected patients that were monitored for their diabetes.

Design, exposure and outcome. This was a cohort study evaluating the association between eGFR and the occurrence of hypoglycaemia during a follow-up period of two years. The study exposure was eGFR as a continuous variable and grouped into six categories (>104, 90-104, 60-89, 30-59, 15-29 and <15 ml/min/1.73 m^2), with eGFR 90-104 ml/min/1.73 m^2 serving as reference. The outcome was the occurrence of hypoglycaemia, defined either by ICD-10

diagnoses or by abnormal glucose measurements. A glucose value between 3 and 3.9 mmol/l, in the absence of a concurrent ICD-10 diagnosis, defined mild hypoglycaemia. If there was a diagnosis of hypoglycaemia, or a blood glucose <3 mmol/l, the event was considered moderate/severe. The reason for classifying all events with a hypoglycaemia diagnosis into the second group, was that we presumed a clinical diagnosis to originate from the manifestations of symptoms of hypoglycaemia, which could be either severe, thereby meeting the criteria for ADA grade 3 hypoglycaemia, or could have prompted corrective measures (i.e. carbohydrate administration, which is usually done at symptom presentation) prior to glucose testing. To avoid misclassification in the case a person received treatment before testing, we disregarded glucose measurements that were concurrent with an ICD-10 diagnosis of hypoglycaemia. We relied on glucose measurements and diagnoses from outpatient care, but included emergency-ward data (collected at hospital presentation), not to miss severe cases of outpatient hypoglycaemia. We excluded glucose measurements from within a 7-day period of a hypoglycaemia event, because, although the resolution of hypoglycaemia is commonly instantaneous, we reasoned that the following days (at least after a symptomatic or severe episode) might be a period of intensified glucose surveillance, which would risk inducing indication bias. We also evaluated the risk of fatal hypoglycaemia associated with eGFR, and defined it as a hypoglycaemia followed by death within seven and thirty days

Statistical analyses. We calculated crude cumulative incidence and adjusted and unadjusted incidence rate ratios of hypoglycaemia (mild or moderate/severe) across eGFR categories. Incidence rate ratios of hypoglycaemia were assessed through zero-inflated negative binomial regression. We tentatively calculated IRR with Poisson regression but, because of over-dispersion, reverted to the negative binomial regression model, which is an extension of the Poisson regression model that allows for over-dispersion (i.e. a variance in the occurrence of events that is greater than the mean) [128]. Zero-inflation is a means of adapting the model to a situation where zero-valued observations are in excess, and therefore un-fit for a Poisson distribution, as was the case in our data of hypoglycaemia occurrences. Adjustments were made for relevant demographics, concurrent medication and co-morbidities, as well as health care use. The relationship between kidney function level and hypoglycaemia (including fatal hypoglycaemia) was graphically depicted by restricted cubic splines.

We identified predictors of hypoglycaemia with the use of ordinal logistic regression. Multiple imputation was carried out for missing values (HbA1c and cholesterol levels were lacking in 21% and 31%, respectively). UACR was missing in too many participants – and most probably not at random – and we decided not to include it our analyses.

Finally, the risk of fatal hypoglycaemia was quantified by Cox' proportional hazards model, adjusting for a restricted number of covariates due to a low number of events.

We did two sensitivity analyses. First, we checked for interaction between eGFR strata, age and sex. Secondly, since all episodes of hypoglycaemia (except those that recurred within one week in the same individual) were counted, any participant could contribute with several counts. As hypoglycaemia recurrence might not be independent of the first occurrence, it risks violating one of the assumptions of the negative binomial regression model, namely that the events occur independently of each other. For this reason, we performed a sensitivity analysis with the Anderson-Gill method, which is an extension of the Cox model, that admits the possibility that recurrent events are determined by prior occurrences [129].

4.2. Ethical considerations

The research we are conducting is entirely laboratory and registry based. Personal data are anonymized and aggregated on a level where backward identification is impossible. The risk of harm towards the individual, or the risk of breaching personal integrity can be considered minimal because there is no contact between investigator and participant. Data storage, after de-identification, was considered safe at the encrypted servers of the department of Medical Epidemiology and Biostatistics, and in compliance with KI regulations. Because many individuals had died at the time of data collection and because the benefits of the research were considered higher than the potential harms, the Ethics committee deemed informed consent by participants to be dispensable.

5 MAIN RESULTS

5.1 The SCREAM project: protocol overview and regional representativeness

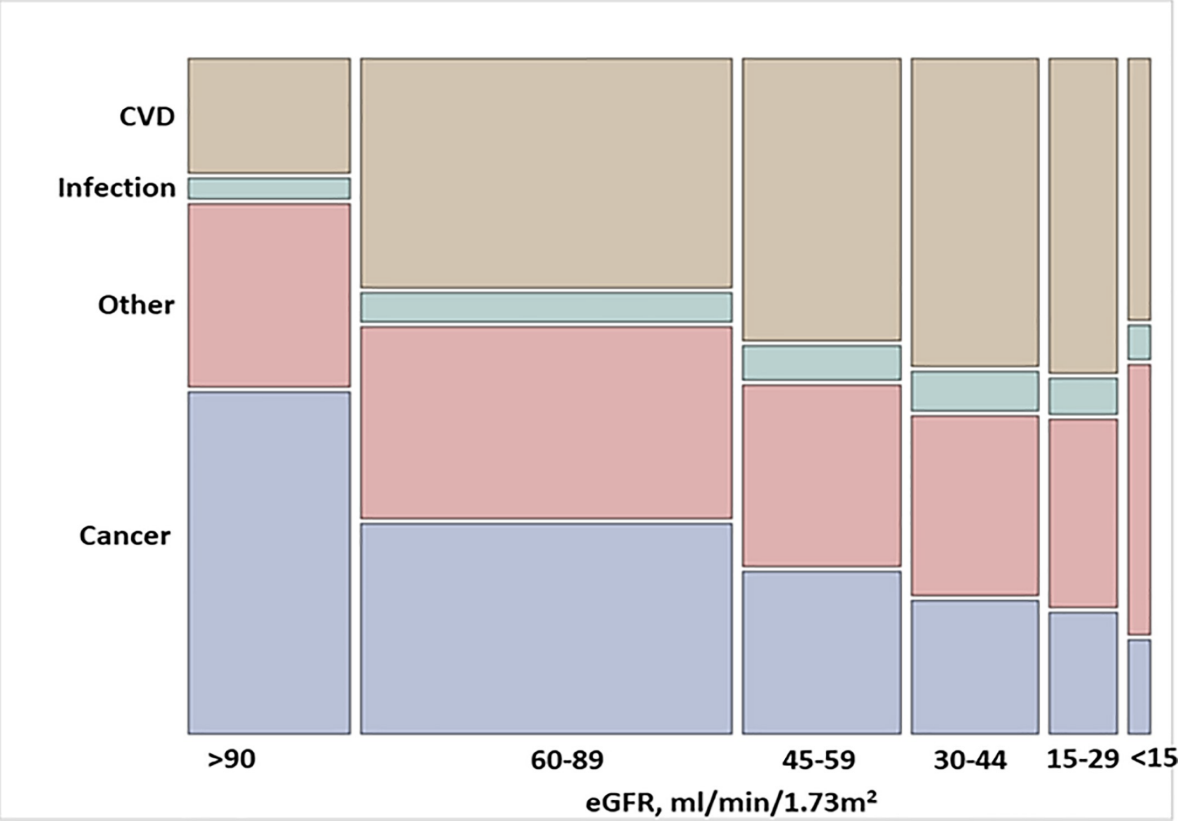
The SCREAM cohort included 1,118,507 individuals, and covered 66% of the adult population of the Stockholm region in the years 2006-20011 (1,706,259 persons aged ≥18 years were censored in the Stockholm region during the study years). The coverage in each municipality ranged between 60 and 70% of censored citizens, mainly depending on the average age of the population living in them and the proximity to other regions (hence the possibility to access healthcare in the nearby regions). As age highly influences the likelihood of creatinine testing, SCREAM captured more than 90% of people aged 65 years or above. Similarly, 98% and 97% of Stockholm residents with a diagnosis of diabetes and cardiovascular disease, respectively, were captured. There was a slightly higher proportion of women in the lower age strata (<65 years) of the SCREAM cohort than in the Stockholm population, but the overall sex distribution was rather similar (in total, 54% women in SCREAM, 51% in the general population). The age

distribution was, predictably, skewed towards the elderly, in whom an indication for testing tends to be more common, with 43% of SCREAM participants, and 55% of the Stockholm population, in the age span 18-44 years. For the same reasons (i.e. greater need of healthcare), SCREAM participants had a higher prevalence of CVD (11% vs 7%) and diabetes (7% vs 5%) than the general population. Of 91,353 deaths registered in Stockholm during 2006-2011, 89% (n=81,270) occurred in SCREAM participants.

5.2 Causes of death across eGFR categories

70.547 persons who died during the data collection period of SCREAM had an eGFR measurement within a year before death. Their median age was 82 years, and 42% had eGFR below 60 ml/min/1.73 m^2. Causes of death varied considerably according to baseline eGFR. The most common cause of death was cardiovascular disease (in 36% of participants), followed by cancer (31%). In people with an eGFR >60 ml/min/1.73 m^2, cancer was the commonest cause of death, whereas CVD was the most common death cause in patients with an eGFR <60 ml/min/1.73 m^2. The proportion of CVD deaths became progressively larger with lower eGFR. Death attributed to infections also became more common in those with eGFR <60 ml/min but did not change significantly across lower eGFR strata (**figure 2**).

Figure 2. Causes of death across eGFR categories



From Runesson et al, PLoS One (2019) [130], reprinted with permission.

A more detailed analysis of cardiovascular causes of death showed ischemic heart disease to change little across eGFR strata, except for a rise in the lowest level (53% of CVD deaths). There was a trend towards higher proportions of heart failure deaths in eGFR <60 ml/min/1.73 m^2.

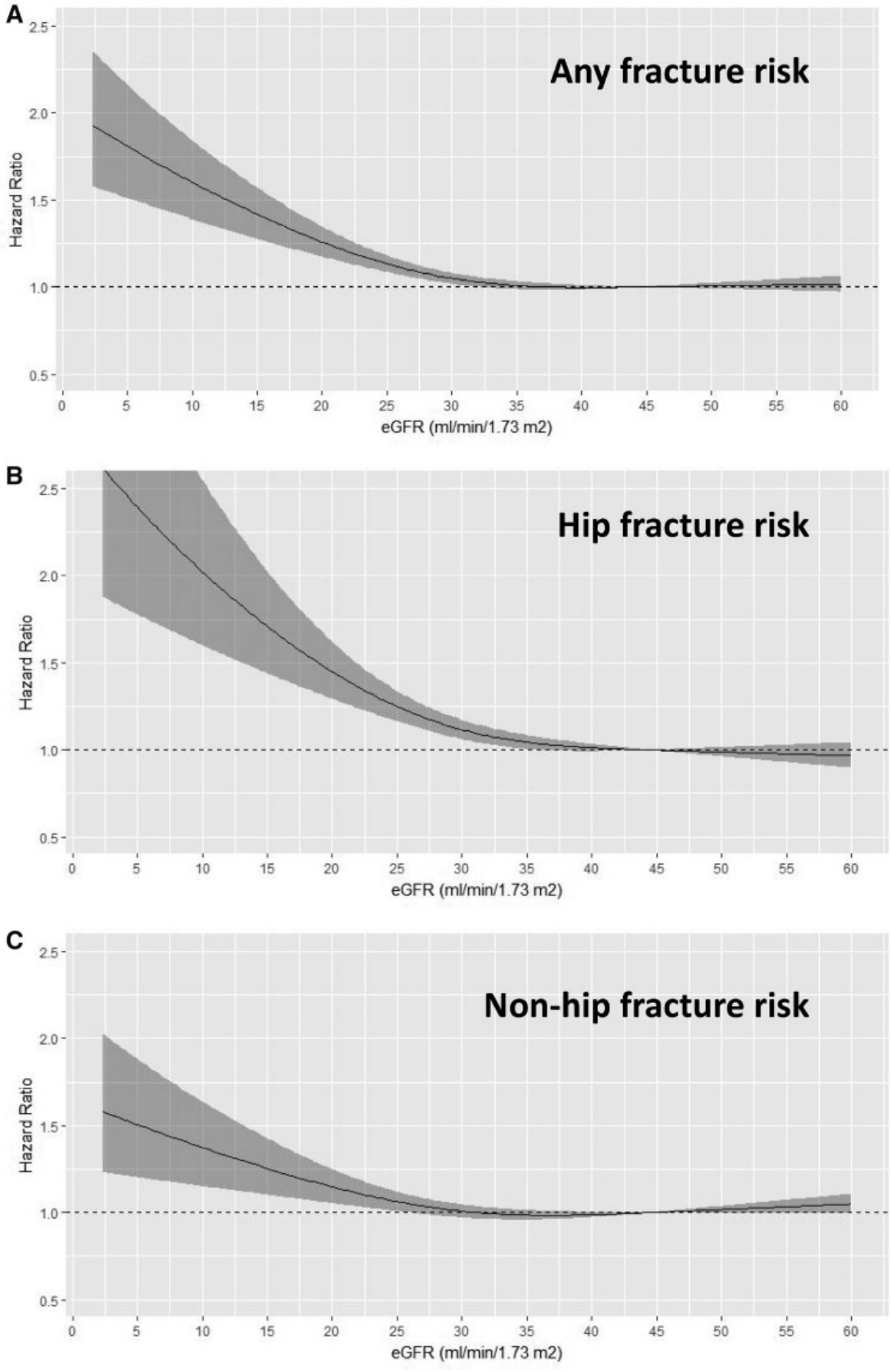
We noted some sex differences. Women had a higher age (median 85 years, vs 80 years in men). Men more often had a diagnosis of diabetes (21% vs 15%) and more often had their death ascribed to ischemic heart disease (46% vs 36%). Accidents and suicides were more common among men. Diabetic complications were more often the cause of death in men, in all eGFR strata. The pattern of death causes across eGFR strata was similar for both sexes.

5.3. Fractures and their sequelae in CKD

This study included 68,764 persons with confirmed CKD stages 3-5. 56% were women, and the median age was 79 years. 706 individuals had CKD 5, but were not on renal replacement therapy (RRT was an exclusion criterion). In all, 9,219 fractures were registered (only the first incident fracture was counted), of which 34% were hip fractures, during the follow-up period

(median 2.7 years). Fracture risk was associated with age, sex (higher for women), eGFR, underlying conditions related to vascular ageing, chronic inflammation and cancer, substance abuse, and the use of loop diuretics, opioids, antidepressants, as well as corticosteroids. The age and sex adjusted hazard ratio for fractures increased for every stage of CKD severity, as compared to CKD 3a. Adjustments for co-morbidities and concurrent medication did not importantly alter this pattern. For instance, compared to CKD stage 3a, the multivariable adjusted hazard ratio for hip fractures and non-hip fractures among persons with CKD stage 5 was 2.47 (1.94- 3.15) and 1.50 (1.25- 1.80), respectively (**figure 3**).

Figure 3. Risk of fractures in relation to eGFR



From Runesson et al, Nephrol Dial Transplant, (2020) [131] with permission.

Suffering a fracture was associated with a higher risk of MACE. The risk was elevated within ninety days of an unspecified fracture (HR 4.0 (95% CI 3.7- 4.3) or a hip fracture (HR 6.3 (95% CI 5.7 – 7.0) . In the long-term (>90 days after developing the fracture), the risk was somewhat attenuated but remained high. Likewise, we observed an excess risk of death following both hip and non-hip fractures.

5.4. Risk of hypoglycaemia in CKD

The study included 29,434 people with type 1 or type 2 diabetes. Their median HbA1c was 6.1 (IQR 5.4-7.1), with minor variations across eGFR strata. 6.2% of the study population had at least one episode of hypoglycaemia in the two years of follow-up. The risk of hypoglycaemia gradually increased with lower kidney function (multivariable-adjusted incidence rate ratio 7.6 (4.8-12) in eGFR <15 ml/min/1.73 m^2 , compared to eGFR 90-104 ml/min/1.73 m^2). The risk of fatal hypoglycaemia also increased with lower eGFR categories. Several predictors of hypoglycaemia were identified, of which reduced kidney function, a history of diabetes complications (including previous hypoglycaemia), liver disease and cerebrovascular disease were the most prominent, along with use of insulin and sulfonyl-ureas.

6 DISCUSSION

6.1 Summary of main findings

This thesis aimed to inform on the epidemic of CKD in the region of Stockholm. Paper 1 describes the creation of the SCREAM cohort, and shows that it covers a representative portion of the regions' population – particularly those with chronic diseases or advanced age. Paper 2 shows that causes of death vary according to patients' eGFR, with a preponderance for cancer in higher eGFR strata and for CVD in those with CKD. Paper 3 describes a higher risk of incident fractures with lower eGFR, and that developing a fracture associates with a higher risk of MACE and death. Paper 4 shows that reduced eGFR associates with a higher risk of both mild and severe hypoglycaemia in persons with diabetes.

6.2 SCREAM coverage and representativeness

6.2.1 Interpretation

Benefiting from the possibility of linking multiple health registers through Sweden's unique personal identification number for all citizens, the SCREAM cohort is to the best of our

knowledge the largest and most comprehensive resource in Sweden to evaluate the burden and impact of CKD on population health. It has a potential value not only for epidemiologists but also for health care planning.

Considering the growing concern, globally, of the increasing number of people with CKD, the low grade of reporting of CKD in disease registries, and the extensive routine sampling of creatinine in health care, administrative health care databases such as SCREAM can be an efficient tool for assessing disease prevalence and quality of care, identify needs, and generate research hypotheses [132].

6.2.2 Strengths and weaknesses

A general impediment to the representability of health care registries is their reliance on health care consumers, which most likely will induce a selection of people that have more health problems than the general population. Accordingly, the SCREAM population, consisting of people with an indication for creatinine testing, has a higher age, and a higher burden of disease than the general population. On the other hand, the high coverage of sub-populations who are more vulnerable to kidney problems is a strength of the SCREAM extraction, making it particularly suited for studies of the effects of CKD.

It might be kept in mind that Stockholm has a younger population than the rest of the country, because of (national and international) immigration, and that average educational and income levels that are higher (Public Health Agency of Sweden, https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/), and might therefore not be representative of the rest of the country.

Health care registries are limited to subjects who have access to health care. This shortcoming is largely reduced by the universal access to healthcare in Sweden, which minimizes socioeconomic determinants in this respect. Nevertheless, we are only able to follow persons that have a valid personal identification number, excluding immigrants that lack legal permit for residency. There might be other boundaries to accessing health care, or determinants of health care consumption, such as educational level, cultural background, presence of mental illness, that could not be accounted for. One limitation is that we did not have information on those residents of Stockholm who did not appear in SCREAM. It is only by comparing the SCREAM cohort with the source population that we can make observations on its' representativeness.

The accuracy of diagnostic codes in routine health care can be variable in both specificity and sensitivity [133-136], limiting the precision of our observations. This limitation is, however, unavoidable in health care registries, and is a random error whose effect is diminished by the size of the study material. Moreover, the use of administrative health care registries can, by combining complementary pieces of diagnostic information, overcome some of the shortcomings of diagnosis registration in routine clinical care (for example in identifying patients with CKD, or diabetes).

A weakness of this database is the lack of information on several important clinical parameters, such as blood pressure, BMI, smoking habits and other life-style factors. Another limitation is that we do not have information on ethnicity. When calculating eGFR, we assumed everyone to be non-black, which might lower the precision of our estimates.

SCREAM contains information on all pharmacy-dispensed prescribed medicines, but not over-the-counter medications, such as NSAIDs, which can influence kidney function and other health outcomes. Nor did we have data on in-hospital drugs or vaccines. This said, over-the-counter drugs are often physician-prescribed in Sweden, for reasons of price reduction for the patient.

As we rely on creatinine-based eGFR in these studies, some inherent fallacies of such estimations need to be acknowledged. Age, an important determinant of GFR, and has been discussed above. The potential contribution of SCREAM in this setting is to ameliorate our understanding of the effects of reduced eGFR on health outcomes in older population segments.

Furthermore, there are several non-renal determinants of creatinine blood levels, such as muscle mass, meat intake, illicit drugs and exercise [27] - that cannot be accounted for in this database. Likewise, eGFR in obese subjects might be less accurate for reasons of deviation from the indexed body surface area [137]. eGFR formulas may lead to underestimations of CKD prevalence, when compared with measured GFR (mGFR) – where actually the clearance of iodinated contrast material (such as iohexol) in plasma is measured – as has been suggested in some European cohorts [27, 138, 139], particularly in the elderly [8]. In the absence of mGFR, which is rarely performed in routine care and only for specific purposes, eGFR is, however, the best available tool for epidemiological surveys of renal function, and has been shown to be as strongly associated to relevant clinical outcomes among CKD patients as mGFR [140].

A drawback of creatinine-based eGFR has been local differences in calibration of creatinine assays that affect estimations [27], but this is overcome by the use of an absolute standard for

creatinine calibration, by isotope dilution mass spectrometry (IDMS) [141], to which the enzymatic and the corrected Jaffé methods, used in our studies, are calibrated. Besides, laboratories providing SCREAM data are regularly monitored for quality and harmonization.

Lastly, there are other eGFR formulas, such as the Lund-Malmö formula, that may be more accurate than CKD-EPI, particularly in a Swedish population [142]; however, since these have not been sufficiently validated in international populations, CKD-EPI continues to be the most widely used, and was therefore chosen for our studies, to facilitate comparisons.

6.2.3 Clinical relevance

The advantages of the SCREAM project are considerable. It allows, for the first time, linkage of extensive laboratory and other health and demographic parameters with dispensed medical prescriptions, presenting unique opportunities for longitudinal studies of drug prescription patterns and health outcomes – in particular those that are not routinely captured in registered medical diagnoses, such as kidney function decline, inappropriate drug prescriptions, drug safety, disease and drug associations.

Up to now, clinical trials have tended to exclude persons with reduced kidney function, creating a demand for studies using real-life data from representative population samples with sufficient clinical parameters at hand. This study shows that SCREAM can serve as a screening tool for the presence and consequences of CKD by making use of existing data, surpassing the requirements of a proper screening program.

The representativeness of SCREAM was high overall, but most so in the population segment aged above 65 years (>90%), and among persons with underlying cardiovascular disease or diabetes (>97%), which will facilitate generalizations in coming studies. This can be compared with for example NHANES III (National Health and Nutritional Examination Survey III) which had an overall response rate of 78% in a sample of the US population (https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx) or the Norwegian HUNT3 (Helseundersøkelsen i Trøndelag 2) study which attained a response rate of 54% [143]. Importantly, these surveys capture a fraction of their source populations, and are based on voluntary participation, which means that there is a risk that people with worse health disproportionally decline to partake [144]. In contrast, SCREAM has a high coverage of people with common chronic diseases, reflecting the availability of a universal health care system.

In conclusion, the SCREAM project is a region representative health care extraction, presenting unique possibilities to study the prevalence of reduced kidney function in society, and how it associates to a variety of health issues.

6.3 Causes of death and kidney function

6.3.1 Interpretation

This study was, to the best of our knowledge, the first to show the variance of causes of death across stages of kidney function in a European population. Death from CVD increased in persons with eGFR <60 ml/min/1.73 m^2, as expected. Less intuitively was that this increase was not solely driven by ischemic heart disease (IHD) deaths, but from a variety of CVD causes, most notably congestive heart failure. Even though IHD may be the underlying cause in many cases, our findings warrant attention to the broad spectrum of CVD manifestations in CKD. Our findings support previous evidence of a strong and bidirectional association between kidney dysfunction and heart failure, and heart failure as a common cause of death in advanced CKD [47, 145, 146]. We also see a trend towards higher proportion of deaths from valvular disease as well, with lower eGFR, in agreement with a previous study from Canada [53], highlighting the importance of arterial calcification in CKD. Infection was a commoner cause of death in persons with eGFR <60 ml/min/1.73 m^2, confirming previous data on infection risk in CKD [52]. The greater prevalence of death from diabetic complications in persons with low eGFR might likewise draw the attention to the importance of diabetes control in CKD.

6.3.2 Strengths and weaknesses

The strengths of this study include a large, region-representative population sample, widespread creatinine testing in the elderly, extensive medical information with no loss to follow-up. This enabled us to expand previous knowledge of cause-specific deaths across kidney function strata.

A limitation of this study is its' cross-sectional nature, preventing us from drawing any causal inferences. We furthermore had no information on those who died without a recent creatinine testing. Findings from this study shoud be understood as hypothesis-generating, and can underline disease-specific associations and risks in CKD.

Another weakness is that we rely on death certificates for establishing causes of death. These have shown questionable accuracy in validation studies [147], with disagreement between clinical and post mortem diagnosis in 25% of cases in Sweden, where autopsies are presently done in only 12% of deaths [148]. This can, however, be regarded as a random error, unrelated to the exposure (pre-mortem eGFR). However, it is also possible that the physician writing the certificate will be influenced by knowledge of pre-mortem kidney dysfunction, and in that way, death certificates might to some extent only confirm unproven assumptions, which risks introducing a systemic bias. With the low degree of autopsies, however, we had no other way of conducting a large-scale study on causes of death. Lastly, we relied on a single GFR estimation, which might not have been representative of the persons' long-term kidney function. Our research interest lay, however, in establishing a clinically relevant association, and not a causative link, between eGFR level and cause of death.

6.3.3 Clinical relevance

The herein featured variation in causes of death according to kidney function estimates might remind clinicians and health care planners to consider cause-specific preventive efforts in persons with declining kidney function. It is already well-known from previous studies, that CKD is a harbinger of higher mortality. The contribution of the present study is to further characterize the forms that this increased mortality takes. For example, an increased proportion of deaths from infection may highlight the ultimate consequences of the observed susceptibility to severe infections in patients with CKD [20]. Likewise, our reporting of a higher share of deaths from heart failure among persons with low kidney function, gives a clue to the considerably elevated CVD fatality burden in this patient group, and underlines the need to monitor and treat patients with CKD for concurrent heart failure.

6.4 Fractures and their sequelae in chronic kidney disease

6.4.1 Interpretation

This study points to an inverse relation between kidney function and fracture risk among persons with confirmed CKD. Compared to CKD stage 3a, the risk is particularly elevated in CKD stages 4 and 5, an observation which is consistent with our understanding of the mineral bone disturbances commonly encountered in advanced CKD. The study also demonstrates an association between incident fractures and adverse cardiovascular events and death among

patients with non-dialysis requiring CKD, which, to our knowledge, is novel. We noted a sex difference, with a higher fracture risk increase, and a higher post hip fracture mortality in men with CKD. We lack a mechanistic explanation for this, but find support for this observation in previous evidence of a higher risk of vertebral fractures among male haemodialysis patients [149], and for a higher post fracture mortality in men in the general population [150]. We believe these findings warrant further investigation. Another intriguing observation was a more pronounced association between eGFR and fracture incidence, and between incident fractures and MACE in persons without diabetes. Although persons with both type 1 and 2 diabetes have a higher risk of fractures, a higher than normal bone mineral density is described in type 2 diabetes, suggesting the presence of other bone quality aberrations in these patients [151]. One could speculate that this higher BMD protects persons with type 2 diabetes and CKD from osteoporotic fractures, but this would require further confirmation.

Our finding of an increased risk of fractures in CKD was partly confirmed in a Swedish study of osteoporotic fractures among elderly women [152], Paradoxically, in their study, fracture risk was lower in more severe stages of CKD. This might be explained by the voluntary participation in that study, with sicker persons, at higher risk of fractures, declining to participate or dying before developing the outcome.

Lastly, our study highlights the importance of fracture prevention in persons with CKD, which also calls for muscle and balance strengthening efforts to reduce the risk of falls which is higher in this patient group [153], and since non-dialysis dependent CKD is associated with a lower lean mass, sarcopenia, and impaired balance [154, 155].

6.4.2 Strengths and weaknesses

The strengths of this study include a large, region-representative sample of patients with confirmed CKD according to KDIGO guidelines, extensive clinical and demographic information, and no loss to follow-up. Besides, using eGFR as a time dependent exposure allowed a person to contribute with time in different CKD categories (as eGFR tends to change over time).

The study yet has some limitations worth mentioning. We had no or scarce information on certain parameters that may have influenced fracture risk, such as vitamin D and PTH levels. Very few participants (1%) had a diagnosis of hyperparathyroidism, indicating an under-reporting of this disease (whose secondary form is common in CKD). However, vitamin D and

parathyroid hormone imbalances are part of the CKD-MBD complex, and may be viewed as mediators between CKD and fractures, not confounders needed to be adjusted for. There were other, mainly life-style risk factors, which ideally would have been adjusted for but on which we did not have information, such as alcohol intake, smoking and BMI. Information on bone morphology or bone mineral density would have been of value, but was outside the scope of this study, as this kind of data is only retrieved in specific patient populations and not yet part of routine clinical care of CKD patients.

We probably have not captured all vertebral fractures, since they are commonly not clinically identified, but require specifically directed radiology [156]. Given the strong risk increase noted between reduced eGFR and incident fractures in general, however, it seems unlikely that a thorough assessment of vertebral fractures would have altered this association - particularly as vertebral fracture prevalence tends to be high in patients with both non-hip fragility fractures and hip fractures [157, 158].

6.4.3 Clinical relevance

These results underline the need for a broader use of fracture prevention and risk assessments, such as the fracture risk assessment tool (FRAX), and BMD measurements, which are both validated for fracture risk prediction in persons with CKD [61, 159]. They also underscore the need for more studies on the treatment and follow-up of osteoporosis in patients with CKD 4-5, that has been noted elsewhere [61, 160]. Moreover, the study speaks in favour of a more vigilant monitoring of patients with CKD who have suffered a fracture, for the occurrence of CVD events.

6.5 CKD and hypoglycaemia in diabetes mellitus.

6.5.1 Interpretation

The study describes a strong and gradual risk association between eGFR and hypoglycaemia in a large cohort of persons with diabetes. This finding was biologically plausible, in view of the well-known alteration of glucose homeostasis that occurs in advanced CKD [109], and therefore not unexpected. But the observed increase in hypoglycaemia risk even in the context of mild eGFR reduction seems to suggest disturbed glucose handling to occur earlier in the course of CKD than was expected. Differences in antidiabetic medication use did not fully explain the risk. Although we cannot exclude residual confounding, we find support for our

observations in some previous studies [117, 161]. Lower kidney function also correlated with the risk of fatal hypoglycaemia (in a time frame of 7 to 30 days).

The clinical predictors of hypoglycaemia that were found in this study emphasizes the link between hypoglycaemia and overall frailty, and underscores the need for close glucose surveillance in the multi-morbid patient with diabetes. These predictors are in accordance with previous research [95] but adds both reduced and increased (>104 ml/min/1.73 m^2) eGFR.

6.5.2 Weaknesses and strengths

A limitation of this study is the lack of data on lifestyle risk factors for hypoglycaemia, such as dietary irregularities and physical exercise. These may theoretically be unevenly distributed across eGFR levels, if, for example, people with higher GFR are more physically active (in which case observed associations could be attenuated), or that loss of appetite and cachexia are commoner in sever kidney disease (which would be a mediator, not a confounder). In any case, lifestyle information would not have been possible to collect for such number of unselected individuals, as are included in this study.

An additional weakness is the lack of some potentially important clinical parameters. Albuminuria has been associated with hypoglycaemia [95], but was seldom measured in our study population, and hence not included as a covariate. More importantly, diabetes duration is a risk factor for hypoglycaemia [117, 162], on which we had no data. Consequently, the increased risk seen with lower eGFR in our study could, to some extent, reflect diabetes duration, given the accelerated loss of kidney function in diabetes [163]. Nevertheless, we adjusted for the presence of diabetes complications (whether identified as such in the ICD coding, or as micro- or macrovascular diseases), which would be expected to correlate with diabetes duration. Besides, even if our observations would be causally unrelated, they still imply a clinically important link between kidney function and hypoglycaemia risk, that might serve to ascertain a more thorough risk assessment on the part of the prescribing physician.

An obvious limitation is that we only retained information on hypoglycaemia to the extent that it came to the attention of health services. However, we did not aim to capture the whole burden of hypoglycaemia in this population, but rather wished to see how it was distributed in relation to kidney function strata. Undetected hypoglycaemia episodes also arguably constitute a random error, particularly as we adjusted for the number of glucose measurements and health care consultations that study individuals underwent.

The study has several strengths, including a large, unselected population of people under routine outpatient treatment for diabetes and with a recent kidney function estimation, a prospective follow-up with far-reaching diagnostic, laboratory and medical prescription data, and results that are robust across subgroups.

6.5.3 Clinical relevance

The importance of this study is that it underlines the impact of kidney function on hypoglycaemia risk, which could guide the choice of therapy of type 2 diabetes in persons with CKD, particularly as the spectrum of antidiabetic agents for this patient category has widened, with the recent label on metformin use at lower eGFR levels [164], and the introduction of newer agents with minimal hypoglycaemia risk, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists [165, 166].

7 CONCLUSION

The present thesis concludes that

1. Cohorts enriched with healthcare-performed creatinine measurements, such as The Stockholm CREAtinine Measuremenst project, can inform studies on CKD epidemics, its management and consequences. Creatinine testing is common in Stockholm healthcare, rendering a good coverage of patients with older age, cardiovascular diseases and diabetes.
2. Causes of death varies across levels of kidney function, with a larger attribution to cardiovascular causes across lower eGFR strata.
3. The risk of fractures is inversely associated with kidney function in polyclinically monitored patients with CKD, and the risk of adverse events and death in the aftermath of a fracture is clearly elevated in both short and longer term.
4. Hypoglycemia risk is higher among persons with diabetes and chronic kidney disease.

8 POINTS OF PERSPECTIVES

This thesis has discussed some implications of the increasing burden of CKD. Aspects that were not incorporated into these studies but that might play a significant role in the epidemiology of CKD, include socio-economic data, which could be a valuable complement in future studies. As demonstrated in this thesis, SCREAM offers a variety of epidemiological study subjects, and is particularly well suited for studies of such exposures and outcomes that often evade clinical attention and diagnosis-based registries.

As has been underscored, fracture prevention, including osteoporosis treatment, in persons with CKD merit more research and clinical attention, and future epidemiological studies should evaluate osteoporosis monitoring, treatment and outcomes in this population. The 2017 KDIGO guidelines on CKD-MBD recommend that CKD patients at risk for osteoporosis (or with signs of CKD-MBD) undergo a BMD measurement, when this might impact treatment decisions [167]. Future investigations can assess the compliance to these recommendations in are observed, and how big proportion of patients with CKD 3b and below are evaluated for fracture risk, how many are treated with an anti-osteoporotic agent?

The interactions between CKD and diabetic complications are worthy of much future research, including studies on the optimal HbA1c level across CKD strata [168], and also the implementation of new treatment recommendations such as a wider use of SGLT2 inhibitors (in eGFR>30 ml/min/1.73 m^2) and GLP-1 receptor agonists for persons with diabetes and CKD [165, 169]. These drugs have exhibited a very low risk of hypoglycaemia in clinical trials [165]: observational studies of these drugs in people with CKD can show whether they reduce the risk of hypoglycaemia in people with CKD and type 2 diabetes in a real-world setting.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING (SUMMARY IN SWEDISH)

Kronisk njursvikt är ett vanligt tillstånd som många har utan att veta om det. Att ha kronisk njursvikt kan få många oönskade följder: risken att drabbas av andra sjukdomar, såsom hjärt-kärl-åkommor, ökar, och medicindoser kan behöva anpassas för att undvika biverkningar. Diagnosen kronisk njursvikt kan ställas genom laboratorieanalyser av blod- eller urinprover. För att ta reda på hur många som har kronisk njursvikt, och för att kunna studera konsekvenserna av detta, skapades en hälsodatabas innehållande laboratorievärden och annan medicinsk information om alla som, i Stockholmsregionen under åren 2006-2011, lämnat blodprover, där ett njurfunktions-värde, kallat kreatinin, ingick. All denna information behandlades anonymt, så att enskilda uppgifter var omöjliga att spåra till någon individ. Med hjälp av denna databas, kallad SCREAM (The Stockholm CREAtinine Measurements project), kunde vi studera både förekomst och ett flertal konsekvenser av kronisk njursvikt, och den låg till grund för samtliga delarbeten i denna avhandling.

I det första delarbetet beskrivs tillkomsten av SCREAM och där konstateras att en stor del av Stockholmsbefolkningen – 66% - har bidragit med information till denna databas. Befolkningsgrupper med hög ålder eller kroniska sjukdomar var i än högre grad representerade i SCREAM (>90% av dem över 65 år, och 98% av personer med diabetes).

I det andra delarbetet undersöks hur dödsorsaker sammanhänger med uppskattad njurfunktion det sista året före döden, och fann att hjärt-kärlsjuklighet, bland annat i form av hjärtsvikt, infektioner och diabeteskomplikationer var vanligare som dödsorsak hos dem med lägre njurfunktion.

Det tredje delarbetet syftade till att ta reda på om, och i vilken grad, lägre njurfunktion ökar risken för benbrott hos personer med kronisk njursvikt. Likaså ville vi se om risken för allvarliga hjärt-kärl-händelser (t. ex. hjärtinfarkt eller stroke) eller död ökade i efterförloppet till ett benbrott. Risken för benbrott befanns öka successivt med avtagande njurfunktion, och risken för allvarliga hjärt-kärl-händelser var även den markant stegrad hos dem som drabbats av benbrott (både höftfrakturer och andra frakturer).

Det fjärde och sista delarbetet var ett utforskande av hur njurfunktion påverkar risken för lågt blodsocker (hypoglykemi) hos personer med diabetes. Hypoglykemirisken visade sig vara högre, ju lägre njurfunktionen var, och det gällde även risken för hypoglykemi med dödlig utgång.

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