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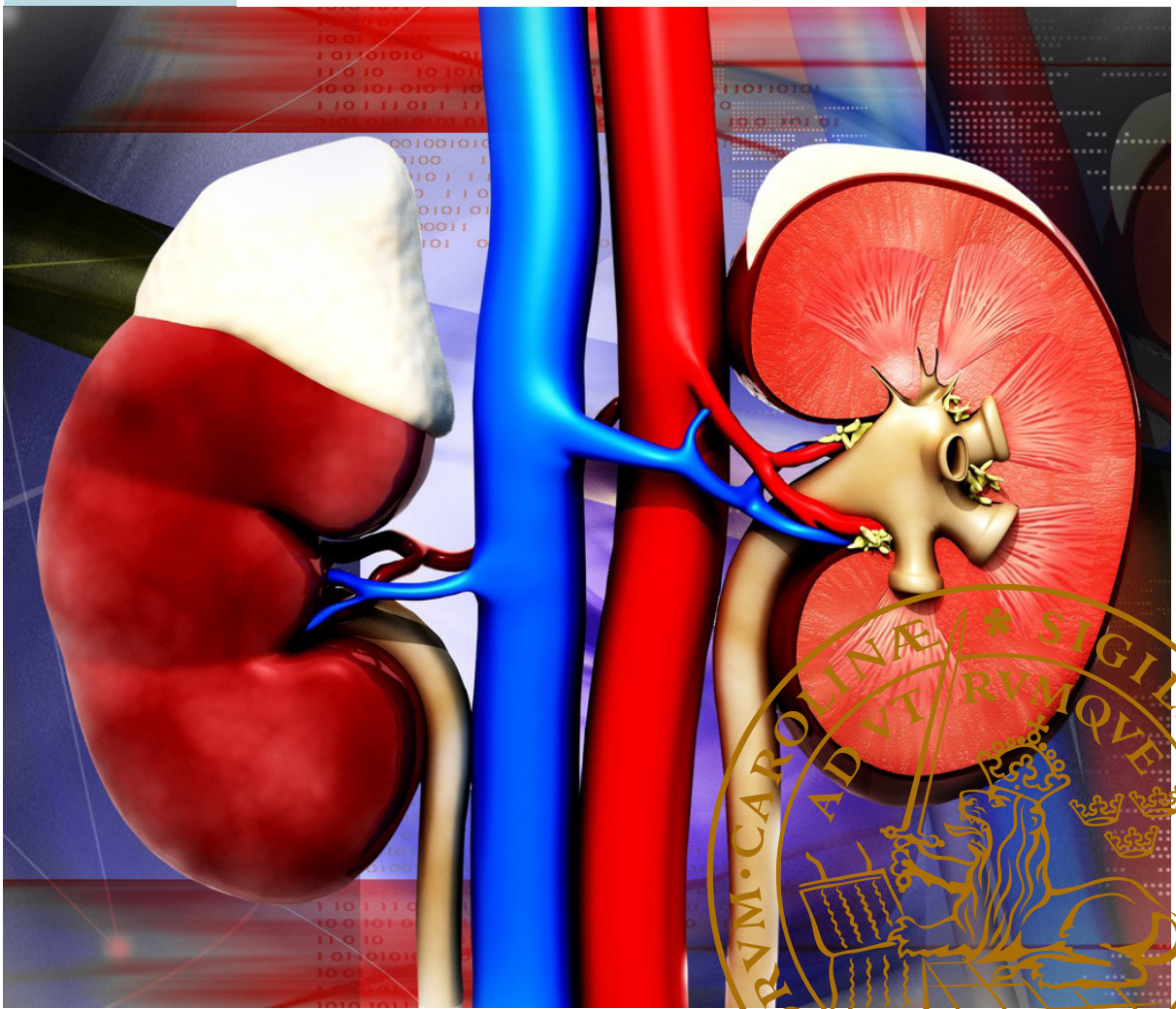

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Kidney diseases are common clinical conditions among all medical specialities. The frequencies of comorbidity and mortality are high. Most of severe kidney failure cases are under uremic treatment with dialysis and or kidney transplantation. In this thesis aspects of familial risks and nonhereditary factors are put to account for kidney failure and glomerulonephritis. Heritability of end stage renal disease is high. Further, the thesis concludes a high hereditary factors impact on chronic kidney failure and glomerulonephritis.

Dr. Delshad Saleh Akrawi is a specialist physician in General Medicine. He graduated from Linköping University, School of Medicine 2002. He worked in internal medicine in early carrier and now has been working in Primary Health Care since 2006. This thesis was completed during the years 2012-2018 at Primary Health Care Research Center, Departement of Clinical Sciences, Malmö, Lund University, Sweden.

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Epidemiology of kidney failure and glomerulonephritis in Sweden

Epidemiology of kidney failure and glomerulonephritis in Sweden:

Hereditary and non-hereditary factors

Delshad Saleh Akrawi

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Epidemiology of kidney failure and glomerulonephritis: Hereditary and non-hereditary factors

Abstract

Background: Kidney disease is recognised as an important worldwide health burden. Kidney failure is the result of acute and chronic kidney disease and is associated with morbidity and mortality. Chronic kidney failure is associated with high-costs for society and low quality of life. Kidney failure may progress to end-stage renal disease (ESRD) that requires dialysis or kidney transplantation with associated high costs for society and low quality of life for the patient. Both genetic and socioeconomic factors are increasingly recognised as important for the development of kidney disease. However, the importance of hereditary and socioeconomic factors has not been studied nationwide in a whole country for kidney failure or glomerulonephritis.

Aims: The overall aim was to study the association between familial and non-hereditary factors and kidney failure and glomerulonephritis in Sweden. In the first paper, neighbourhood deprivation and ESRD was studied. In the second paper, familial risks of renal failure was determined. In the third paper, familial risks of glomerulonephritis was studied. In the fourth paper, heritability of ESRD was determined among Swedish adoptees.

Methods: The thesis is based on nationwide retrospective cohort studies using Swedish registers such as the Multi-generation register and the National patient register (NPR). In the first paper, data were analysed by multilevel logistic regression, with individual-level sociodemographic factors and comorbidities at the first level and neighbourhood deprivation at the second level. In the second and third papers familial relative risks (FRRs) of kidney failure and glomerulonephritis were determined using standardized incidence ratio (SIR). In study IV logistic regression (OR=odds ratio) and tetrachoric correlation and also Falconers regression were used to determine heritability of ESRD among adoptees in Sweden.

Results: In paper I, neighbourhood deprivation was modestly associated with ESRD in the full model after adjusting for individual-level sociodemographic factors and comorbidities in men OR=1.17 (95% confidence interval [CI] 1.07–1.27) and in women OR=1.18 (95% CI 1.06–1.31). In paper II the FRR was significantly increased for chronic kidney failure (SIR= 2.02, 95% CI 1.90-2.14) but not for acute kidney failure (SIR=1.08 (95% CI 0.94-1.22) and for unspecified kidney failure, i.e. not specified as acute or chronic (SIR=1.25 (95% CI 0.94–1.63). Males and females had similar FRR for chronic kidney failure, (males SIR=2.04 [95% CI 1.90-2.20] versus females SIR=1.97 [95% CI 1.78-2.17]). The highest FRR was observed for chronic kidney failure among individuals aged 10-19 years (SIR=6.33 [95% CI 4.16-9.22]). In paper III FRR for acute glomerulonephritis was 3.57 (95% CI 2.77-4.53), for chronic glomerulo-nephritis 3.75 (95% CI 2.85-4.83), and 3.75 (95% CI 2.85-4.83) for unspecified glomerulonephritis, i.e. not specified as acute or chronic. An especially high FRR was observed if two or more relatives were affected (SIR=209.83, 95% 150.51-284.87). In paper IV odds ratio (OR) for ESRD was 6.41 (95% CI 2.96-13.89) in adoptees with a biological parent diagnosed with ESRD. The odds ratio for ESRD was not significantly increased in adoptees with an adoptive parent diagnosed with ESRD (OR=2.40, 95% CI 0.76-7.60). The heritability of ESRD was 59.5 ± 18.2%.

Conclusion: Family history of chronic kidney failure and glomerulonephritis are important risk factors for kidney diseases. Heritability of ESRD is high. Familial factors were not associated with acute kidney failure to any major degree. Genetic factors are indicated to be of importance for the burden of glomerulonephritis and chronic kidney failure and in the Swedish population. In contrast, neighbourhood deprivation is only associated with a modestly increased risk of ESRD.

Keywords: Kidney failure, glomerulonephritis, heredity, epidemiology

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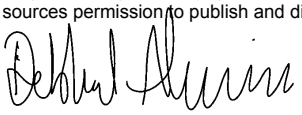
Signature  Date 2018-04-16

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Dedicated to my Father Saleh, my Mother Aisha and My family

Table of Contents

List of publications

This thesis is based on the following papers referred to in the text by their Roman numerals:

I. Akrawi DS, Li X, Sundquist J, Sundquist K, Zöller B. End stage renal disease risk and neighbourhood deprivation: a nationwide cohort study in Sweden. Eur J Intern Med 2014; 25:853-9.

II. Akrawi DS, Li X, Sundquist J, Sundquist K, Zöller B. Familial risks of kidney failure in Sweden: a nationwide family study. PLoS One 2014; 9: e113353.

III. Akrawi DS, Li X, Sundquist J, Fjellstedt E, Sundquist K, Zöller B. Familial risks of glomerulonephritis - a nationwide family study in Sweden. Ann Med 2016; 48:313-22.

IV. Akrawi DS, Pirouzifard MN, Sundquist J, Fjellstedt E, Sundquist K, Zöller B. Heritability of End-stage renal disease: A Swedish adoption study. Nephron 2018; 138: 157-165.

Abbreviations

AAN	Anti-neutrophil cytoplasmic antibody-associated nephritis
APOL1	Apolipoprotein L1
AT1	Angiotensin 1
ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
^{51}Cr-EDTA	Chromium - ethylene diamine tetracetic acid
95% CI	95% confidence interval
BMI	Body Mass Index
COL4A3	Collagen type III alfa 3 chain
COL4A4	Collagen type IV alfa 4 chain
COL4A5	Collagen type V alfa 5 chain
CVD	Cardiovascular disease
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease-Epidemiology Collaboration
CNI	Care Need Index
eGFR	estimated Glomerular Filtration Rate
EPO	Erythropoietin
ESRD	End stage renal disease
FRR	Familial relative risk
GWAS	Genome wide association study
GFR	Glomerular Filtration Rate
HR	Hazard ratio
ICC	Intra Class Correlation
ICD	International classification of diseases
IPR	The Swedish National Inpatient Register
KVÅ	Klassifikation av vårdåtgärder
L	Litre

MDRD	Modification of diet in renal disease
MYH9	Myosin heavy chain 9
NPR	National patient register
PRKAG2	Protein kinase AMP-activated – non-catalytic subunit gamma 2
OR	Odds ratio
RAAS	Renin-Angiotensin-Aldosterone system
SAMS	Small area market statistics
SD	Standard deviation
SE	Standard error
SES	Socioeconomic Status
SLE	Systemic Lupus Erythematosis
SHROOM3	A gene associated with kidney diseases
SIR	Standardized incidence ratio
TPR	The Swedish total population register
UMOD	Uromodulin
WHO	World Health Organization

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Background: Kidney disease is recognised as an important worldwide health burden. Kidney failure is the result of acute and chronic kidney disease and is associated with morbidity and mortality. Chronic kidney failure is associated with high-costs for society and low quality of life. Kidney failure may progress to end-stage renal disease (ESRD) that requires dialysis or kidney transplantation with high costs for society and low quality of life for the patient. Both genetic and socioeconomic factors are increasingly recognised as important for the development of kidney disease. However, the importance of hereditary and socioeconomic factors has not been studied nationwide in a whole country for kidney failure or glomerulonephritis.

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Chapter I.

Introduction

Background

The burden of kidney disease has been targeted for discussions in recent decades (Levin et al 2017). Chronic kidney disease (CKD) affects 10-15% of the population worldwide; the cause of CKD is multifactorial. Chronic kidney diseases are of great clinical importance because of the strong effect of such diseases on life expectancy, morbidity, low quality of life for the patient, and high costs for the society (Levin et al 2017).

Epidemiology is the science devoted to the study of frequency, distribution, and causes (determinants) of health and disease at a population level (Ahrens & Pigeot, 2005). Results from epidemiological studies may be used for disease prevention and control. In the present thesis, the epidemiology of kidney failure and glomerulonephritis in Sweden was investigated. The importance of sociodemographic factors (paper I) and hereditary factors (papers II and IV) in kidney failure was determined. Glomerulonephritis is one of the most common causes of kidney failure including end-stage renal disease (ESRD) (Chadban & Atkins, 2005). Familial risks for glomerulonephritis were also determined (paper III). The heritability of ESRD was studied in paper IV.

Anatomy and physiology of the kidney

The bean-formed kidneys (latin renes, singularis ren) are positioned behind the peritoneum with one kidney on each side of the spinal column (Fogo et al, 2006). Each kidney weighs approximately 150g and is about 12cm long, Figure 2. The kidneys receive 20% of cardiac output (about 1.1 L/min) from the renal arteries. The blood is filtered through the renal capillaries and the renal glomeruli to form the primary urine. The normal glomerular filtration rate (GFR) is about 125 mL/min, which corresponds to 180 Litres (L) a day (Lote, 2012). Most of the formed primary urine is absorbed during the transport in the tubular system. The

final urine amount is approximately 1500mL. The functional unit of the kidney (the glomeruli and its connecting tubular system) is called “the nephron”, Figure 1.

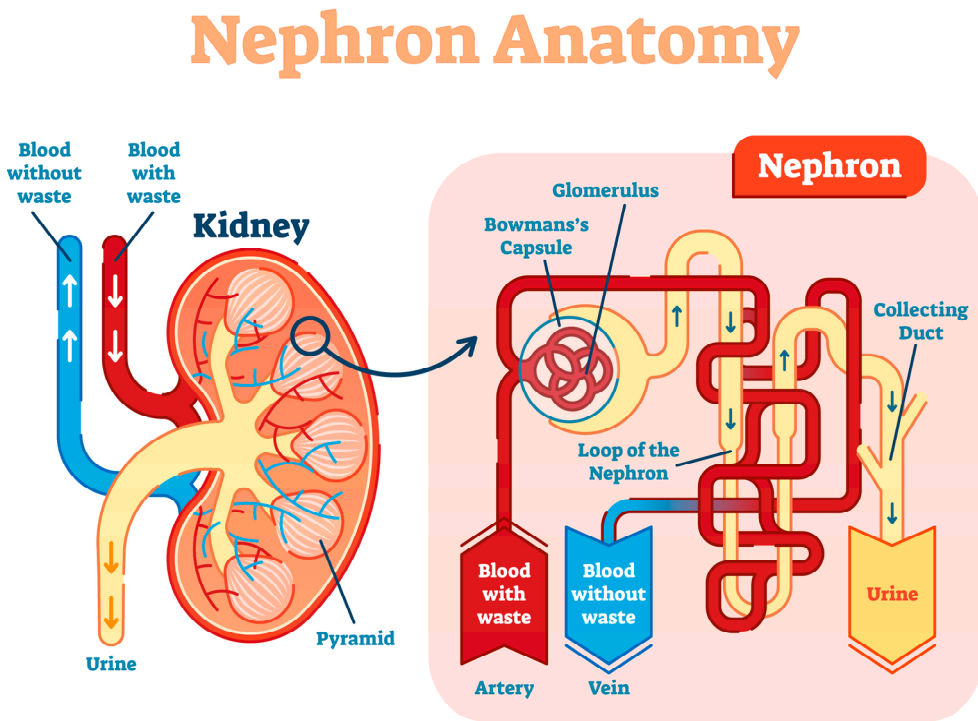


Figure 1
Illustration of nephron

The kidneys play a key role in homeostasis, i.e. maintenance of the equilibrium of the body’s internal environment necessary for a normal cellular function (Lote, 2012). The kidneys regulate the balance of water, electrolytes, acid-base status, small molecules, and blood pressure. Another important function of the kidneys is to remove metabolism waste products. The kidneys also have endocrine functions and produce erythropoietin (EPO), calcitriol (1,25-dihydroxycholecalciferol), and the enzyme renin (Lote, 2012). The kidneys form and secrete EPO in response to hypoxia at the cellular level. Erythropoietin is necessary for normal red blood cell production in the bone marrow. Calcitriol is the active form of vitamin D. Renin is secreted from juxtaglomerular cells and enzymatically cleaves angiotensinogen to angiotensin I. The enzyme angiotensin converting enzyme (ACE) thereafter converts angiotensin I to angiotensin II, which in turn binds and activates the type 1 angiotensin II receptor (AT1). The activation of AT1 increases blood pressure due to vasoconstriction but also aldosterone secretion. Aldosterone increases the reabsorption of sodium ions from the tubular fluid in exchange to excretion of

potassium ions into the tubular fluid. This renin–angiotensin–aldosterone system (RAAS) is an important regulator of the plasma sodium concentration and arterial blood pressure. The RAAS is also the target for modern antihypertensive treatment with ACE inhibitors and angiotensin receptor blockers (ARBs) (Li et al, 2014).

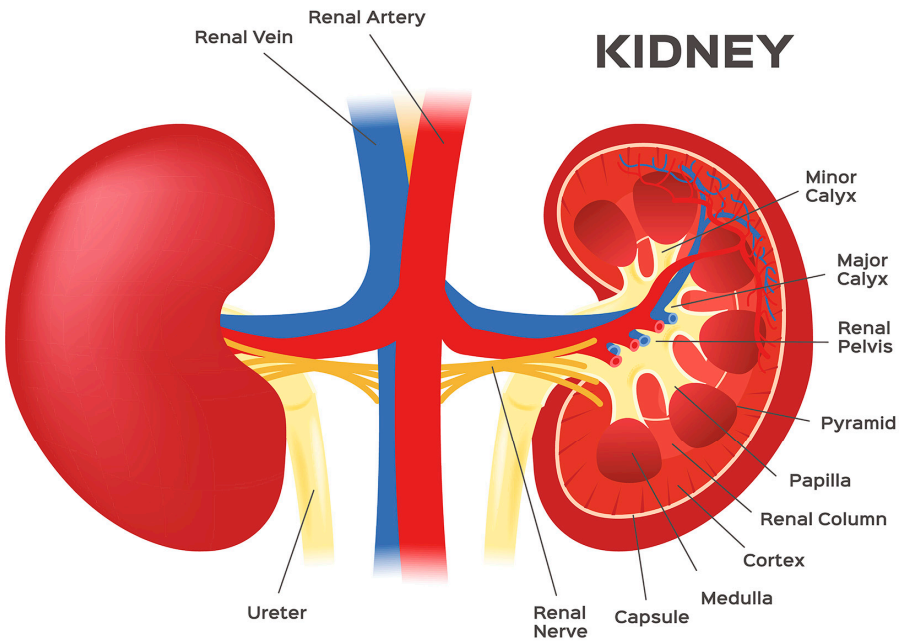


Figure 2
Illustration of kidney anatomy.

The most widely accepted measure of kidney function is GFR (Levey et al, 2014). The GFR is determined by the product of the filtration rate in a single nephron and the number of nephrons in the two kidneys. The mean value of GFR is 120-130 mL/min/1,73 m^2 for adults younger than 40 years of age. GFR decreases with age. GFR can only be measured indirectly by analysing the excretion of exogenous filtration markers like inulin, iohexol (plasma iohexol clearance), ^{51}Cr-EDTA or estimated (eGFR) from serum levels or from endogenous filtration markers such urea, creatinine, and cystatin C. Ideally, a filtration marker should be inert (small enough to be freely filtered) not protein bound, not reabsorbed or secreted in the tubule, not metabolised by the kidney, and easy to measure. However, all methods are associated with some form of error and the 'true' GFR cannot be exactly determined (Levey et al, 2014; Perrone et al, 1992; Stevens et al, 2006).

Creatine is formed non-enzymatically from muscle creatine at a fairly stable rate (Perrone et al, 1992). The molecular mass of creatinine is 113 Dalton. It is freely filtered by the glomerulus. Previous studies support the similarity of creatinine clearance to GFR and its reciprocal relationship with serum creatinine level (Stevens et al, 2006). Proximal cells in the glomeruli secrete the creatinine. The tubular secretion of creatinine varies within and among individuals. Moreover, certain drugs like trimethoprim and cimetidine inhibit creatinine secretion, which leads to reduced creatinine clearance and elevated serum creatinine levels without affecting the GFR (Stevens et al, 2006). The formation of creatinine is otherwise mainly determined by muscle mass and dietary intake, which is believed to cause the observed variation in serum creatinine by gender, age, geographic, ethnic, and racial groups (Stevens et al, 2006).

Equations have been developed to estimate GFR from serum creatinine by taking into account variables like age, gender, race, and body size to adjust for differences in muscle mass (Levey et al, 2014; Stevens et al, 2006; Evans et al, 2013). Estimating equations may therefore overcome some of the limitations with serum creatinine measurements. The two most common equations used to determine eGFR are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and the Modification of Diet in Renal Disease (MDRD) study equation, which are both based on creatinine measurement. Cystatin C based CKD-EPI equations have also been developed. Other equations used to estimate GFR are Cockcroft-Gault, Mayo Clinic equation, and the Lund-Malmö equation. Equations that include multiple endogenous glomerular filtration markers have been shown to be more exact in estimating GFR than equations that use only a single glomerular filtration marker (Levey et al, 2014).

Renal failure

Kidney or renal failure occurs when the kidney cannot maintain homeostasis, which results in accumulation of nitrogen containing metabolites (azotaemia) (Remer et al, 2014). The exact clinical and biochemical criteria, however, remains to be precisely defined. Kidney insufficiency usually means an abnormal kidney function that is, however, sufficient to sustain important body functions. Renal failure can be classified according to urine production: <50mL for 24 hours is called anuric kidney failure, <500mL for 24 hours is called oliguric kidney failure, while urine volume between 500mL to 6000ml for 24 hours is called non-oliguric kidney failure. If the urine volume is above 6000mL for 24 hours it is termed polyuric (Remer et al, 2014). The causes of kidney failure can be divided into three principal different categories: prerenal failure (hypoperfusion for instance due to fluid loss, septic or cardiac shock, or renal artery stenosis), intrarenal failure

(i.e. tubular, interstitial, glomerular, or small-vessel kidney disease), and postrenal failure (obstruction for instance due to prostate hyperplasia, stone, or cancer).

Another important distinction is between acute renal failure and chronic renal failure (Remer et al 2014; Drum, 2013). Nowadays the term acute kidney injury (AKI) is usually preferred over acute renal failure and chronic kidney disease (CKD) is preferred over chronic renal failure. The incidence rate of AKI is not well established but studies have suggested an increased incidence from 61 to 288 per 100000 individuals from 1988 to 2002 (Cerdá et al, 2008). In developed countries, mostly elderly people develop AKI while in low-income countries AKI is common in young individuals due to infections, toxins, or obstetric and surgical complications. Whether genetic factors are involved in AKI has yet to be determined (Cerdá et al, 2008; Remuzzi et al, 2013).

The CKD criteria have developed over time. The current international definition of CKD is lowered kidney function with a GFR <60mL/min/1.73m^2 or markers of kidney damage (albuminuria ≥30mg/g, abnormal urinary sediment, electrolyte or other abnormality due to tubular disease, abnormal histology, image detected structural abnormalities, or history of kidney transplantation), or both with duration of at least three months (Webster et al 2017). CKD is usually divided into five classes. Patients with CKD-1 have normal GFR (≥90 mL/min/1.73m^2) but persistent albuminuria (albuminuria ≥30mg/g). Patients with CKD-2 have mildly decreased GFR (60-89 mL/min/1.73m^2), CKD-3 patients have mild to severely decreased GFR (30-59 mL/min/1.73m^2), CKD-4 patients have severely decreased GFR (15-29 mL/min/1.73m^2), and CKD-5 patients have severe kidney failure (<15 mL/min/1.73m^2). End-stage renal disease (ESRD) denotes severe CKD that makes dialysis or transplantation necessary in order to maintain long-term lifespan (Remer et al, 2014).

The prevalence of CKD is around 11% in affluent countries. The three most common causes of CKD in middle to high-income countries are diabetes (30-50%), hypertension, and glomerulonephritis (Webster et al, 2017). The prevalence of CKD exhibits variations associated with ethnicity and socioeconomic factors. Both environmental influence and genetic factors are associated with CKD (Webster et al, 2017).

Important issues to highlight are to slow progression of CKD and to reduce albuminuria in order to prevent ESRD development. ESRD is associated with morbidity, mortality, and high cost for dialysis and transplantation treatment. Fast rates of GFR decline have been observed in patients with high concentrations of albuminuria, diabetes, or hypertension (Levey & Coresh, 2012). Such treatments are angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), usually in association with diuretic drugs but also intensive glycaemic control in patients with diabetes (Levey & Coresh, 2012).

Sociodemographic factors and kidney diseases

Socioeconomic status (SES) is a measure of an individual's occupational, economic, and social position in relation to other individuals, based on income, education, and occupation. Health and diseases are not evenly distributed across SES (Fiscella & Williams, 2004). Not only individual low SES has been associated with worse health and mortality but also the neighbourhood environment is associated with morbidity and mortality (Pickett & Pearl, 2001). Methods for combining group level and individual level data, i.e. hierarchical regression analysis (multilevel), have been developed and are frequently used. Multilevel analysis separates the effect of social environment (contextual effect) from individual level SES (compositional effect). A critical review by Pickett & Pearl (2001) found a consistent compositional effect but also a fairly consistent but more modest contextual effect on health. Why persons of lower SES have unhealthier lifestyles is both an important and an unanswered question (Cohen et al, 2003). Poverty has been associated with smoking, alcohol consumption, and high-fat diets. Some unhealthy types of behaviour cost money, which suggests that the unhealthier lifestyles are not always due to an absolute lack of money (Cohen et al, 2003). Other related issues such as a low level of support and social capital have also been implicated (Lindström M, 2004; Cohen et al, 2003). Moreover, poor neighbourhood might also, per se, affect health through mechanisms such as ‘‘collective efficacy’’ (i.e. a measure of willingness to help out for the common good) and ‘‘broken windows’’ (boarded up stores and homes, litter, and graffiti) (Cohen et al, 2003). However, contextual effects (neighbourhood) tend to be generally modest and much smaller than compositional effects (individual level SES) (Pickett & Pearl, 2001).

CKD has been associated with SES such as income, educational attainments, wealth, and occupation (Rostand et al, 1989; Perneger et al, 1995; Krop et al, 1999; Fored et al, 2003; Crews et al, 2010). Several studies have also shown that living in a deprived neighbourhood is associated with CKD (Wittle et al, 1991; Brancati 1992; Young et al, 1994; Byrne et al, 1994; Merkin et al, 2005; Ward, 2008; Bello et al 2008; Volkova et al 2008). However, only a few studies have adjusted for individual-level SES (Merkin et al, 2005; McClellan et al, 2010; Merkin et al, 2007; Shoham et al, 2008). Merkin et al (2005) found an association between CKD and neighbourhood after adjustments only for white men and not for white women, African-American women, and African-American men. McClellan et al (2010) found an association between CKD and household poverty but not with deprived communities. Among elderly people aged above 65 years, deprived neighbourhood was independently associated with CKD (Merkin et al, 2007). Shoham et al (2008) found no association with CKD and deprived neighbourhood over the lifecourse. Thus, the results of the studies for

neighbourhood deprivation and risk of CKD, independent of individual level SES, is not consistent and not easy to interpret. It is also not known if comorbidities affect these associations. In the present thesis, Akrawi et al (2014) have shown that local area poverty (contextual effect) is associated with CKD independent of individual level SES (compositional effects) and comorbidities. Shared familial environmental exposures and lifestyle factors may be of importance for disease development, and not only inherited biological factors.

Genetics and kidney failure

Aggregation of a disease in families may indicate a genetic cause but also non-genetic familial factors may contribute (Burton et al, 2005). However, a genetic cause is unlikely if a disease does not aggregate in families, which is a key concept in genetic epidemiology; Family studies are therefore important. In order to disentangle genetic from non-genetic familial factors, several methods are possible: twins, adoptees, and extended family studies (Burton et al 2005; Risch, 2001). Heritability is the quantification of the phenotypic variation that is attributable to genetic factors, i.e. a ratio of variance components (Lee et al, 2011).

Family history of ESRD was first reported by Ferguson et al (1988) to be common among African-Americans with ESRD. Several case-series and case control studies have confirmed the importance of family history of CKD and/or ESRD to be associated with CKD (Freedman et al, 1993; Lei et al, 1998; O'Dea et al, 1998; Bergman et al, 1996; Jurkovitz et al, 2002; McClellan, 2007; Jurkovitz, 2005; McClellan, 2007; Jurkovitz et al, 2005; Freedman et al, 1997; Freedman et al, 2005). A follow-up study by Hsu et al (2009) found a modestly increased hazard ratio (1.40) of self-reported family history of kidney disease for development of ESRD. No studies have determined whether familial and genetic factors are involved in AKI.

In the present thesis, Akrawi et al (2014) have shown that chronic kidney failure aggregates in families, while AKI is not or only weakly related to inherited factors. Moreover, in an adoption study, the heritability of ESRD (defined as patients with chronic dialysis or kidney transplantation) was determined to be 59.5% ± 18.2% (Akrawi et al, 2017). In a heritability study of ESRD from Taiwan that included patients with dialysis but also less severe cases with CKD (International classification of disease 9 [ICD-9] code 585) heritability was 31.1% (Wu et al, 2017). The FFR was 2.46 (95% CI, 2.32-2.62).

Since the first genome wide association study (GWAS) in CKD in 2009 by Köttgen et al more than 50 different genes have been associated with CKD (Piras et al, 2017). However, most of these loci are weakly associated with CKD and are

not likely to explain all the heritability of CKD. Two main genes identified by GWAS are the UMOD gene and the SHROOM3 gene (Piras et al, 2017). The UMOD gene encodes for uromodulin (Tamm-Horsfall protein). Only epithelial cells of the loop of Henle synthesise this kidney specific protein. Common variants in UMOD are associated with hypertension, eGFR, ESRD, CKD, and kidney stones. UMOD gene defects are associated with kidney diseases like medullary cystic kidney disease-2, familial juvenile hyperuricaemic nephropathy, and glomerulocystic kidney disease with hyperuricaemia and isosthenuria. Thus the UMOD gene is associated with both monogenic kidney diseases and CKD traits. The SHROOM3 gene encodes for an actin-associated protein that is needed for the normal podocyte cytoarchitecture. (Piras et al, 2017).

Glomerulonephritis

Glomerulonephritis (Figure3) is the second most common cause of CKD (Segelmark & Hellmark, 2010). The name glomerulonephritis is used for a group of diseases with histological inflammation of the glomeruli. Immune mechanisms are important for all forms of glomerulonephritis though all forms of glomerulonephritis may not be considered to be autoimmune disorders. Despite pathophysiological advances, treatments for glomerulonephritis are non-specific and only partly successful. Glomerulonephritis is therefore a common cause of ESRD (Chadban & Atkins, 2005).

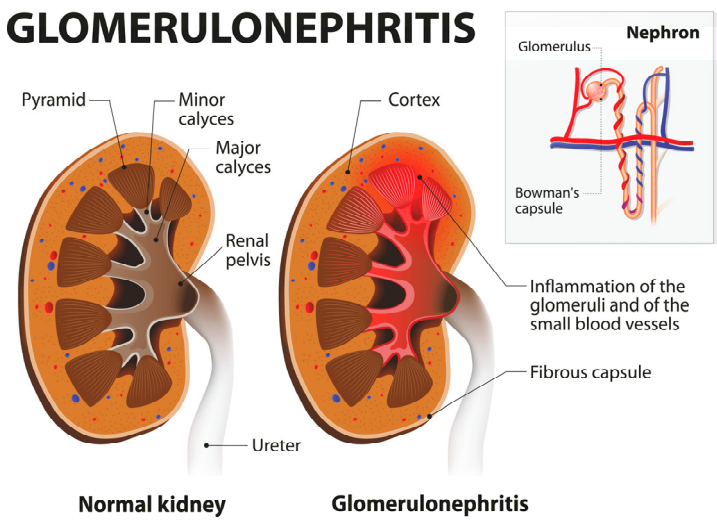


Figure 3
Graphic illustrating a normal kidney and in a kidney affected by glomerulonephritis.

The symptoms of glomerulonephritis range from asymptomatic patients with hypertension, proteinuria by dipstick, haematuria, and raised serum creatinine concentrations to severely symptomatic patients with massive weight gain due to oedema with nephrotic syndrome, and to rapidly progressive glomerulonephritis with uraemia (Floege & Amann, 2016). A kidney biopsy is required for a secure and definitive diagnosis of glomerulonephritis. The most common form of glomerulonephritis in wealthy countries is IgA nephropathy. The annual incidence rates have been estimated to be 2.5 per 100 000 individuals for IgA nephropathy, 1.2 per 100 000 for membranous glomerulonephritis, 0.6–0.8 per 100 000 for minimal change disease and focal segmental glomerulosclerosis, and 0.2 per 100 000 for membranoproliferative glomerulonephritis. However, these numbers are likely to be underestimated (Floege & Amann, 2016). Males are more prone to develop glomerulonephritis than females (Chadban & Atkins, 2005). In low-income countries, children are at an increased risk to develop glomerulonephritis after streptococcal throat or skin infections. Patients with chronic infections such as hepatitis B, hepatitis C, and HIV have increased odds for developing glomerulonephritis. Genetic factors are also involved, for instance Alport's syndrome with mutations in the COL4A5, COL4A3, or COL4A4 genes, with defective collagen type IV. Glomerulonephritis might also be caused by Goodpasture's disease or anti-glomerular basement membrane disease that is due to deposition of anti-glomerular (anti-GBM) basement antibodies (Hellmark & Segelmark, 2014). The resultant complement activation initiates a neutrophil dependent inflammation. Goodpasture's disease is considered the archetype for an autoimmune disease (Hellmark & Segelmark, 2014). Glomerolunephritis may also be due to immune-mediated diseases like anti-neutrophil cytoplasmic antibody-associated nephritis (AAN), systemic lupus erythematosis (SLE), microscopic polyangiitis, granulomatosis with polyangiitis (Wegener), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (Mohammad et al, 2015; Jennette & Nachman, 2017).

Genetics and Glomerulonephritis

Glomerulonephritis is known to aggregate in families (Rambausek et al, 1993; Izzy et al, 2006; Scolari et al, 1992). Among patients with glomerular disorders like Alport's syndrome, steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis, single gene defects have been identified (Hildebrand, 2010). However, single-gene disorders are not common in the general population. Less is known about common variants for glomerulonephritis though such variants have been found in the UMOD, PRKAG2, APOL1 and MYH9 genes (Eckardt et al, 2013). A typical finding for polygenic disorders is that they cluster in families but

do not follow classical Mendelian inheritance patterns (Lander & Schork, 1994). Polygenic disorders also often exhibit a recurrence risk ratio (λ) of around two among first-degree relatives (Burton et al, 2005). The recurrence risk ratio in a polygenic disease (complex trait) is dependent on age of onset, degree of relatedness, number of affected relatives, and severity of disease (Burton et al, 2005; Lander & Schork, 1994). In this thesis, Akrawi et al reported the FRR in first-degree relatives determined with standardised incidence ratio (SIR) (Akrawi et al, 2016). The FRR was 3.57 (95% confidence interval, 2.77-4.53) for acute glomerulonephritis, 3.84 (95% confidence interval, 3.37-4.36) for chronic glomerulonephritis, and 3.75 (95% confidence interval, 2.85-4.83) for unspecified glomerulonephritis (i.e. not acute or chronic) (Akrawi et al, 2016). Very high familial risk was observed in families if two or more relatives were affected (SIR=209.83).

Chapter II.

Aims

General aim

The aim of this doctoral thesis was to study the association between hereditary and non-hereditary factors with kidney failure and glomerulonephritis in a nationwide context.

Specific aims

Paper I: Chronic kidney disease has been associated with socioeconomic disparities and neighbourhood deprivation. The aim was to determine whether there is an association between neighbourhood deprivation (contextual effect) and end stage renal disease (ESRD), and whether this association was independent of individual-level sociodemographic factors (compositional effect) and comorbidities.

Paper II: The value of family history as a risk factor for kidney failure has not been determined in a nationwide setting. The aim was to determine familial risks for kidney failure in Sweden.

Paper III: Familial risks of glomerulonephritis (acute-, chronic and unspecified glomerulonephritis [i.e. not specified as acute or chronic]) have not been studied. The aim was to determine the familial risks of glomerulonephritis.

Paper IV: To evaluate the FRR and heritability of ESRD in adoptees with a biological parent affected by end stage renal disease. Heritability (h^2) determined with Falconer's regression.

Chapter III.

Material and Methods

Design

In this thesis the study design consisted of nationwide retrospective cohort studies (or historic cohort study) where several Swedish nationwide registers were used. An overall view of the four papers and the design of these papers is presented in table 1.

Table 1.
Overview of the papers included in this thesis and their design

	Paper I	Paper II	Paper III	Paper IV
Design	Retrospective Cohort Study	Retrospective cohort study	Retrospective cohort study	Retrospective Cohort study
Participants	5593516	8054071	8187887	37,486
Data	Register data	Register data	Register data	Register data
Analysis	Multi-level Logistic Regression	Standardised incidence ratio SIR	Standardised incidence ratio SIR	Logistic regression and Falconer's regression
Follow-up	2001-2010	1987-2010	1964-2010	1964-2012

Registers used and source of data

The data sources in this thesis were multiple national Swedish data registers including: The Swedish National Population and Housing Census, the Total Population Register, the Swedish Hospital Register (the Hospital Discharge Register and the Hospital Outpatient Register), and the Multi-Generation Register. Statistics Sweden (SCB=statistiska centralbyrån) and the National Board of Health and Welfare (Socialstyrelsen) provided these registers. All register linkages were performed using the individual national identification number that is assigned to each person in Sweden for their lifetime (Ludvigsson et al, 2009). This number was replaced by SCB with a serial number in order to ensure anonymity.

The Swedish Multi-Generation Register

The Swedish Multi-Generation register was provided by Statistics Sweden. The Multi-Generation register constitutes a part of the Total Population Register. The Multi-Generation register includes index persons who have been registered in Sweden at some point in time since 1961 and who were born in 1932 or later. Information is provided for 97% of mothers and 95% of fathers of index persons. The register links around 10 million index persons with their biological parents. Adopted index persons are also linked to their adoptive parents. The Multi-Generation register includes around 150 000 adopted index persons with links to their adoptive parents. From the 2002 version onwards, information is also collected for certain index persons from older national registration material. Every year, a new version of the Multi-generation register is constructed and includes new index persons who immigrated or were born during the year. Information from the Multi-Generation register can be obtained for statistical or research purposes (Statistics Sweden, 2011; Ekbom, 2011).

The Swedish cancer register

The Swedish Cancer Register was started in 1958 and covers the whole Swedish population. The proportion cancer cases that are not reported has been estimated to be less than 2%. Moreover, 99% of registered cancer cases are morphologically diagnosed. It is mandatory for all health care providers in Sweden to report newly discovered cancer cases to the registry (Barlow et al, 2009).

Cause of death register

The Swedish National Board of Health and Welfare provided the Swedish cause of death register. It contains the cause of all deaths in Sweden since 1952. The number of deaths in the register is almost complete. However, the cause of death is missing in a small proportion of deaths (0.9%). There is generally a good parity between death certificate and hospital discharge condition (Mattsson & Wallgren, 1984; Johansson et al, 2009).

The Total Population Register

The Swedish total population register (TPR) was provided by Statistics Sweden. The TPR maintains data such as birth, death, name change, marital status, family relationships, education, migration within Sweden, and migration to and from other countries. Within 30 days, practically 100% of births and deaths, 95% of

immigrations, and 91% of emigrations are reported to the Population Registers. Over time these numbers are even higher (Ludvigsson et al, 2016).

The Swedish National Patient Register

The Swedish national patient register (NPR) consists of The Swedish National Inpatient Register (IPR), also called the Hospital Discharge Register, that was started in 1964 in some regions of Sweden in order to obtain information on inpatient care. The IPR reached nationwide coverage in 1987. In 2001, data on hospital-based outpatient care were added. Coverage of the IPR is almost 100%. However, coverage of hospital-based *outpatient* care is lower (about 80%). Data from private caregivers are missing but coverage of public outpatient care is almost 100%. Primary health care does not report to the NPR.

The information available in NPR consists of type of data: patient related data, patient data (such as personal identity number, age at discharge, sex, and place of residence), data about caregiver (hospital, type of department), administrative data (date of admission, date of discharge, length of stay, unplanned/planned admission, mode of admittance and discharge), and medical data (main and additional diagnosis, external cause of injury or poisoning, and surgical and non-surgical procedures.

Validation of the IPR by the National Board of Health and Welfare showed that 85-95% of all diagnoses in the IPR are valid (Ludvigsson et al, 2011).

Material and methods study I

Design

This study included residents in Sweden aged 20 to 69 years at the start of the follow-up (January 1, 2001). The data consisted of individual- level information concerning age, sex, education, occupation, geographic region of residence, hospital diagnoses, and dates of hospital admissions in Sweden, date of emigration, and date of death.

Sources of data were several national Swedish data registers: the TPR, the Multi-Generation Register, and the NPR. The registers were provided by Statistics Sweden, and the National Board of Health and Welfare (Ekbom, 2011; Ludvigsson et al 2011; Zöller B, 2013). The constructed dataset includes ESRD events for the entire Swedish population, individual-level SES and neighbourhood-level SES (Zöller B, Li X et al 2012, Zöller B, Li X et al 2013, Li

X, Sjöstedt C et al 2014). The main diagnoses of ESRD recorded in the Hospital Discharge Register and Outpatient Register and surgical codes for renal transplantation and dialysis were used. We linked these diagnoses to national census data to recruit data on individual- level SES and geographical region of residence, date of death, and date of immigration or emigration. The individual national identification number was replaced with a serial number by Statistics Sweden in order to ensure anonymity. Period of follow-up started on January 1, 2001 and continued until diagnosis of ESRD, death, emigration, or the end of the study period (December 31, 2010).

Outcome (dependent) variable

ESRD (the outcome variable), based on the 10th revision of the International Classification of Diseases (ICD) or the Classification of Surgical Procedures, defined ESRD as N18.5 (i.e. CKD stage 5), T82.4, Y84.1, Z49, Z94.0, and Z99.2 (ICD-10 codes for ESRD, dialysis or transplantation), and V9211, V9212, V9200, V9531, V9532, V9507, KAS00, KAS10, KAS20, KAS40, KAS50, KAS60, KAS96, KAS97, JAK10, TJA33, TJA35, and TKA20 (surgical codes for transplantation or dialysis). The frequencies of diagnoses for ESRD at presentation are shown in Table 2.

Table 2.
Frequency of diagnostic codes (ICD-10) and procedure and surgery codes in the definition of end stage renal disease (ESRD) at first presentation in the Swedish Hospital Discharge Register and Outpatient Register (2001-2010).

Included conditions in the outcome variable	ICD codes and surgery and procedure codes	No.	%
	ICD-10 code		
CKD, stage 5	**N185**	**950**	**7.7**
Mechanical complication due to dialysis catheter	T824	82	0.7
Preparation for dialysis	Z490	1143	9.3
Extracorporeal dialysis	Z491	1856	15.0
Peritoneal dialysis	Z492	297	2.4
Renal transplantation	**Z940**	**3074**	**24.9**
Dependent on dialysis	Z992	38	0.3
Surgery and procedure code			
Laparotomy and insertion of peritoneal dialysis catheter	JAK10	361	2.9
Autologous renal transplantation	KAS00	10	0.1
Homologous kidney transplant (from deceased donor)	KAS10	822	6.7
Homologous kidney transplant (from living donor)	KAS20	554	4.5
Excision of transplanted kidney	KAS40	40	0.3
Pyelostomy of the transplanted kidney	KAS50	1	0.0
Operation of lymphocele after kidney transplantation	KAS60	2	0.0
Other operation associated with renal transplantation	KAS96	10	0.1
Other percutaneous endoscopic operation in conjunction with a kidney transplant	KAS97	14	0.1
Percutaneous insertion of peritoneal dialysis catheter	TJA33	1108	9.0
Removal of peritoneal dialysis catheter	TJA35	195	1.6
Puncture of lymphocele after kidney transplantation	TKA20	15	0.1
Use of artificial kidney	V9200	5	0.0
Hemodialysis, acute	V9211	357	2.9
Hemodialysis, chronic	V9212	1012	8.2
Construction of tunneled dialysis catheter	V9507	197	1.6
Peritoneal dialysis, chronic	V9531	197	1.6
Peritoneal dialysis, acute	V9532	8	0.1
	All	**12348**	**100.0**

ESRD defined by chronic dialysis and kidney transplantation

To further ensure the accuracy of the definition of ESRD with inclusion of only the most severe cases with ESRD,(i.e. chronic dialysis and kidney transplantation), ESRD was redefined and used in paper I (Table 3) as in paper IV. The new definition of more severe ESRD used in paper IV is presented in Table 3. We have used this definition to do recalculations for papers II and I that are presented here in this summary of the published papers.

Table 3.
International classification of diseases (ICD) and surgical (and non-surgical) intervention codes used to define end-stage renal disease (ESRD) (chronic kidney dialysis or transplantation) defined as chronic kidney dialysis or transplantation used in paper IV but also for additional complementary analysis for study I and II.

	1997 - 2012	**1987 - 1996**	**1969 - 1986**	**----**
	ICD-10	ICD-9	ICD-8	ICD-7
Chronic dialysis	Z49, Z992	V45B, V56	Y29,01	----
Kidney transplantation	T861, Z940	V42A	----	----
Surgical codes version 6, included also non-surgical intervention (1963-1996)				
Kidney transplantation	6043,6070,6071,6072,6073,6077,6079			
Chronic dialysis	9212, 9314			
Surgical intervention codes (KVÅ) 1997-2012 (Non-surgical intervention codes 2007-2012)				
Kidney Transplantation	KAS10, KAS20, KAS40, KAS50, KAS60, TKA20			
Chronic dialysis	DRO12, DRO13, DR016, DR024			
Temporary codes for non-surgical interventions used (TÅL) 1997-2006				
Chronic dialysis	V9212, V9531			

Individual-level variables

Sex, age at the start of the study, marital status, family income, education level, country of birth, urban/rural status, mobility and comorbidities were individual-level variables:

Sex: male or female.

Age: 20 to 69 years (continuous variable).

Marital status: married/cohabitating or never married/widowed/divorced.

Family income by quartile: Income was categorised into quartiles: low income, middle–low-income, middle–high income, and high income. Information came from TPR, this information is provided by Statistics Sweden.

Education level: Completion of compulsory school or less (≤9 years), practical high school or some theoretical high school (10–12 years), and theoretical high school and/or college (12 years).

Country of birth: Born in 1) Sweden (reference), 2) Finland, 3) Western countries, 4) Eastern European countries, 5) Middle Eastern countries, and 6) other countries.

Urban/rural status: Residence in large cities (Stockholm, Gothenburg, and Malmö), middle-sized towns, and small towns/rural areas.

Mobility: length of time lived in neighbourhood, categorised as ≤ 5 years (moved) or ≥5 years (not moved).

Comorbidity: First diagnosis (main or additional diagnosis) during the study period was defined as comorbidity using ICD-10: 1) chronic lower respiratory diseases (defined J40-J49), 2) obesity (defined E65-E68), 3) alcoholism and alcohol- related liver disease (defined F10 and K70), 4) hypertension (defined I10-I15), 5) diabetes mellitus (defined E10-E14), 6) ischaemic heart disease (defined I20-I25), and 7) acute kidney failure (defined N17).

Neighbourhood-level SES

All home addresses for residents in Sweden have been geocoded to small geographical units with boundaries defined by homogeneous types of buildings. These neighbourhood areas were created in 1994 by Statistics Sweden. These neighbourhood areas are called small area market statistics (SAMS) and are inhabited with an average of 1000 people in each SAMS. In the present neighbourhood study, SAMS were used as proxies for neighbourhoods just as in previous research (Cubbin et al, 2006). SAMS with fewer than 50 people aged 25–64 (n=1053) and individuals whose addresses could not be geocoded to a neighbourhood area (n = 83,230 individuals, 13% of the sample) were excluded. The overall total number of SAMS were 8372.

A neighbourhood index was calculated in order to characterise neighbourhood-level deprivation (Winkleby et al, 2007). The neighbourhood index is based on information on women and men aged 20–64 who lived in the neighbourhood because people in this age group are the most socioeconomically active, as a population group they have a larger effect on the socioeconomic structure of the neighbourhood compared to children, younger people, and retired people. Four aspects are included in the index: 1) low education level (<10 years of education), 2) low income (income from all sources defined as less than 50% of the median individual income), 3) unemployment (full-time students, those completing compulsory military service, and early retirees were excluded) and 4) receipt of social welfare. The following three neighbourhood groups were defined (higher index scores reflect more deprived neighbourhoods): low neighbourhood deprivation (more than 1 SD below the mean), moderate neighbourhood deprivation (within 1 SD of the mean), and high neighbourhood deprivation (more than 1 SD above the mean) (Winkleby et al, 2007).

Statistical analysis

Age-adjusted cumulative incidence rates were determined by direct age standardisation using 10-year age groups. The entire study population of women or men in 2001 constituted the standard population. We used Multi-level (hierarchical) logistic regression models to estimate the outcome variable ESRD.

We used Multi-level logistic regression models as they give a good approximation of Cox proportional hazards models if the sample size is large, the incidence is low (less than 5%), and the risk ratios are less than two (Callas et al, 1998). The analyses were performed using MLwiN version 2.27.

Firstly, a neighbourhood model including neighbourhood-level deprivation was created to determine the crude odds of ESRD by level of neighbourhood deprivation. A second model included neighbourhood- level deprivation and age; a third model also included the other individual-level sociodemographic variables (added simultaneously to the model). In the full model, it was determined whether neighbourhood-level deprivation was significantly associated with ESRD after adjustment for individual-level sociodemographic factors and comorbidity (Goldstein H, 2003).

White males but not females had a higher risk of CKD in lower SES neighbourhoods in the Atherosclerosis risk in community study (Merkin SS et al, 2005). Men and women were therefore analysed in separate models. The effects of neighbourhood-level deprivation on risk ESRD across individual-level SES (income and education) categories were studied for multiplicative interaction to determine the presence of effect modification. A low degree of correlation between the factors included in the models was observed. Intraclass correlation (ICC) or variance partition coefficient (VPC) was determined, though not presented in paper I but are presented here in this summary. The ICC shows how much of the variance of ESRD in the population that could be attributable to contextual neighbourhood factors or to the different composition of neighbourhoods.

Material and methods study II

Design

Several national Swedish registers were used. The registers were provided by the Swedish government-owned statistics bureaus (Statistics Sweden and the National Board of Health and Welfare) (Rosen M, Hakullinen T, 2005). Information on family relationships for index persons born in Sweden in 1932 and later were obtained from the Swedish Multi-generation register (Ekbom, 2011). Subjects born in 1932 or later and who were alive in 1987 constituted the present study population. In order to obtain individual-level socioeconomic status, connections were made to the Swedish cause of death register (1987-2010), to the Swedish outpatient care register (2001-2010), and to the Swedish hospital discharge register (1987-2010). The hospital discharge register has had nationwide coverage since

1987. The individual national identification number was replaced by a serial number in order to preserve anonymity; this was done by Statistics Sweden. We used the serial numbers to check that each individual was entered only once. Approximately 8.1 million persons and their biological parents (3.8 million families) were included in the dataset. The oldest included persons (born 1932) were 78 years of age at the end of the follow-up period.

Definition of predictor and outcome variables

Family history (in a sibling or parent) of kidney failure (defined with ICD-codes below) between 1987 and 2010 was defined as a predictor variable. Familial risks for offspring and siblings were determined. First event (main or secondary diagnoses) of kidney failure (acute kidney failure, chronic kidney failure, unspecified kidney failure) in the Swedish hospital discharge register, the Swedish outpatient register, or the Swedish cause of death register was defined as an outcome variable.

Acute kidney failure was defined by ICD codes (main and secondary): 584 (ICD-9) and N17 (ICD-10). Unspecified kidney failure (i.e. not classified as acute or chronic) was defined by ICD codes: 586 (ICD-9) and N19 (ICD-10). Chronic kidney failure was defined by ICD and surgical codes: 585,V45B, and V56 (ICD-9); N18, N26, T82.4, Y84.1, Z49, Z94.0, and Z99.2 (ICD-10); 6070, 6071, 6072, 6073, 6077, 6079, 9211, 9212, 9213, 9314, and 9200 (dialysis or kidney transplantation related surgical codes for 1987-1996); and V9211, V9212, V9200, V9531, V9532, V9507, KAS00, KAS10, KAS20, KAS40, KAS50, KAS60, KAS96, KAS97, and JAK10, TJA33, TJA35, TKA20 (dialysis or kidney transplantation related procedure and surgical codes for 1997-2010).

We excluded individuals with cystic kidney disease (Q61, ICD-10; and 753B, ICD-9), congenital kidney and urinary tract malformations (Q60, Q62, Q63, Q64, ICD-10; and 753A, 753C, 753D, 753E, 753F, 753G, 753H, 753W, 753X, ICD-9), urolithiasis (N20-N23, ICD-10; and 592, ICD-9), rare inherited kidney diseases such as Alports syndrome and Laurence Moon-Biedl-Bardet syndrome (Q87.8A, Q87.8B, ICD-10), and hyperoxaluria (E74.8B, ICD-10; and 271W, ICD-9).

The ICD-10 code N18.1 represents CKD-1, i.e. proteinuria with normal kidney function. However, this diagnosis constitutes 0.02% of all N18 ICD-10 codes in the hospital discharge register and 0.06% in the outpatient register. The inclusion of N18.1 ICD-10 therefore has a negligible effect on the results. Moreover, N18.2 ICD-10 codes reflects CKD-2, i.e. a very mild decreased kidney function with GFR of 60-89 mL/min. However, the N18.2 code also constitutes only 0.04% of all N18 ICD-10 codes in the hospital discharge register and 0.14% in the

outpatient register. Thus, the inclusion of the N18.2 ICD-10 code has a negligible effect on the results.

To further ensure the accuracy of the definition of chronic kidney failure with inclusion of only the most severe cases with ESRD, i.e. chronic dialysis and kidney transplantation) we used this definition in paper IV. The definition of more severe ESRD used in paper IV is presented in Table 4. We have used this definition to do recalculations for papers I and II that are presented here in this summary of the published papers.

Individual variables

Variables included were: 1) Sex: males/female; 2) Age: Age at diagnosis, categorised into 5-year groups; 3) Time period: Divided into 5-year intervals in order to adjust for changes in incidence rates over time; 4) Socioeconomic status: defined by occupation, which was divided into six groups: farmers, blue-collar workers, white-collar workers, professionals, self-employed workers, and others (economically inactive individuals including unemployed individuals and homemakers); 5) Geographic region of residence was divided into three groups: large city, i.e. Stockholm, Gothenburg, or Malmö; Southern Sweden (excluding the large cities, all of which lie in Southern Sweden); and Northern Sweden; and 6) Comorbidity. Comorbidity: main or secondary diagnosis during follow-up between 1987 and 2010, ICD-codes in the Swedish hospital discharge register or the Swedish outpatient care register: 1) chronic obstructive pulmonary disease (490-496 (ICD-9) and J40-J47 (ICD-10)); 2) obesity (278A and 278B (ICD-9) and E65 and E66 (ICD-10)); 3) alcoholism and alcohol-related liver disease (291, 303, 571A, 571B, 571C, and 571D (ICD-9) and F10 and K70 (ICD-10)); 4) diabetes mellitus (250 (ICD-9) and E10-E14 (ICD-10)); 5) hypertension (401-405 (ICD-9) and I10-I15 (ICD-10)); 6) coronary heart disease (410-414 (ICD-9) and I20-I25 (ICD-10)); 7) heart failure (428 (ICD-9) and I50 (ICD-10)); 8) hyperlipidaemia (272A, 272B, 272C, 272D, and 272E (ICD-9) and E78.0, E78.1, E78.2, E78.3, E78.4, and E78.5 (ICD-10)); and 9) stroke (430-438 (ICD-9) and I60-I69 (ICD-10)).

Statistical Analysis

Familial risks of acute, chronic, and unspecified (i.e. not classified as acute or chronic) kidney failure were analysed as described by Hemminki K et al (2001). The method takes into account clustering within families, since it is based on complete ascertainment of sibships in affected individuals. Person-years at risk (the number of persons at risk multiplied by the time at risk) was determined from the start of the follow-up on 1 January 1987 until diagnosis for kidney failure,

death, emigration, or the end of the follow-up (31 December 2010) (Breslow & Day, 1987).

We calculated the age-adjusted incidence rates for the follow-up period, divided into 5-year periods (Breslow & Day, 1987). SIR (standardized incidence ratios) were used to measure the relative risk of kidney failure in individuals with one or more parent with a history of kidney failure compared with individuals with parents without a history of kidney failure. Calculations were also performed for siblings.

The familial risks (SIRs), the ratio of observed (O) and expected (E) numbers of kidney failure cases were calculated. Indirect standardisation method was used:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

where $O = \sum o_j$, the total observed number of cases in the study group; E^* (the expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; o_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by cross-classification of the following adjustment variables: age (5-year groups), sex, socioeconomic status, time period (5-year groups), geographic region of residence, and comorbidities. 95% confidence intervals (95% CIs) were calculated. Values of the data are accurate to two decimals places. Statistical analyses were performed using SAS version 9.2 (Institute, Cary, NC, USA).

Material and methods study III

Design

Nationwide Swedish registers were provided by the Swedish government-owned statistics bureaus, Statistics Sweden, and the National Board of Health and Welfare and were used in the present study (Rosen & Hakullinen, 2005; Ekbom, 2011; Ludvigsson et al 2011; Zöller, 2013). The study population constituted of subjects aged 0-78 years of age. Several nationwide registers were connected to each other to obtain the dataset: National Census data (in order to ascertain individual-level socioeconomic status), the Swedish cause of death register (1964-

2010), the Swedish outpatient care register (2001-2010), and the Swedish hospital discharge register (1964-2010). The Swedish hospital discharge register has had complete nationwide coverage since 1987. The national personal identification number that is assigned to residents in Sweden for their lifetime was replaced by a serial number in order to preserve anonymity (Ludvigsson et al, 2009). In total, approximately 8.1 million individuals and their biological parents (3.8 million families) were included; the oldest individuals, who were born in 1932, were 78 years of age at the end of the follow-up period (2010).

Predictor and Outcome variables

Family history (in a full-sibling and/or parent) of glomerulonephritis between 1964 and 2010 was defined as the predictor variable. The use of the Swedish Multi-generation register eliminates recall bias. Separate familial risks were also determined for offspring and full-sibling history of glomerulonephritis. We defined full-siblings from the Multi-generation register as having the same mother and father. We excluded the subjects without any full-sibling alive any time during the follow-up period (1987-2010) in this analysis. Spouse risk was also determined as a measure for shared familial environment. Spouses were defined as individuals older than 25 years with a common oldest child. Spouses without children were excluded from the analysis. First main or secondary diagnosis of glomerulonephritis (acute-, chronic-, and unspecified glomerulonephritis) in the Swedish hospital discharge register or the Swedish outpatient care register was defined as outcome variable according to: Acute glomerulonephritis was defined by ICD codes (international classification of diseases): 590 (ICD-7), 580 (ICD-8-9), and N00-N01 (ICD-10). Unspecified glomerulonephritis defined by ICD codes: 593 (ICD-7), 583 (ICD-8-9), and N05 (ICD-10). Chronic glomerulonephritis was defined by ICD codes: 592 (ICD-7), 582(ICD-8-9) and N03 (ICD-10). The main causes for hospitalisation and secondary diagnoses were considered. Patients with secondary glomerular diseases (N08) were not included, for instance, glomerular disease due to different types of infections, diabetes and malignancies. Isolated haematuria (N02) or isolated proteinuria (N06) were also not included in order to increase specificity of glomerulonephritis diagnosis and to include those patients that fulfil the clinical diagnosis of glomerulonephritis with more severe phenotype than just isolated haematuria or isolated proteinuria. Moreover, N04 (nephrotic syndrome), and N07 (Nephropathia hereditaria non alibi classificata) were not included.

Individual variables included

In this analysis we included the following variables: 1) Gender: males/females; 2) Age: age at diagnosis categorised into five-year groups; 3) Time period: Period was divided into five-year intervals; 4) Socioeconomic status: Socioeconomic status: occupation for both males and females, which was divided into six groups: farmers, blue-collar workers, white-collar workers, professionals, self-employed workers, and others (economically inactive individuals including unemployed persons and homemakers); 5) Geographic region of residence was divided into three groups: (1) Southern Sweden; (2) large cities; and (3) Northern Sweden. Municipalities with a population of >200,000 were defined as large cities and comprised the three largest cities in Sweden: Stockholm, Gothenburg and Malmö.

Statistical Analysis

A previously described method was used to calculate the risks of familial aggregation in individuals with glomerulonephritis (Zöller B, et al 2011; Hemminki K et al, 2001). The method is based on clustering within families with complete ascertainment of sibships in affected individuals. We also calculated the person-years at risk (i.e. the number of persons at risk multiplied by the time at risk) from the start (1 January 1964) until diagnosis for glomerulonephritis, death, emigration, or the end of the follow-up (31 December 2010) (National Board of Health and Welfare, 2000). We calculated the age-adjusted incidence rates for the follow-up period, divided into five-year periods (Breslow & Day, 1987). To measure the relative risk of glomerulonephritis in individuals with one or more parents with a history of glomerulonephritis, we used the standardised incidence ratios (SIR) compared with individuals with parents without a history of glomerulonephritis. For full-siblings, we performed calculations separately.

The familial SIRs calculated as the ratio of observed (O) and expected (E) numbers of glomerulonephritis cases using the indirect standardization method:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

Where $O = \sum o_j$ denotes the total observed number of cases in the study group; E^* (the expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ^*_j) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; o_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J

represents the strata defined by cross-classification of the following adjustment variables: age (five-year groups), sex, socioeconomic status, time period (5-year groups), and geographic region of residence. 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution (Breslow & Day, 1987).

Familial SIRs for males were compared directly with those for females through calculation of SIR ratios according to the method described by Breslow & Day (1987). The ratios of SIR represent the relative risks for familial glomerulonephritis in males compared with females. SIR ratios have the same interpretation as the relative risk parameters estimated in case-control studies. They represent the ratios of age-specific rates for different exposure categories. Data values are accurate to two decimals places. Analyses were performed using SAS version 9.3 (Institute, Cary, NC, USA).

Material and methods study IV

Design

In this study, collected data were used for adoptees and their biological parents (1964-2012). Several national Swedish registers were used for the analysis: The Swedish Multi-Generation register, national patient register, cause of death register, and the total population register (Rosen & Hakullinen, 2005; Ekbom, 2011; Ludvigsson et al 2011; Zöller, 2013). Statistics Sweden and the National Board of Health and Welfare maintain the registers used in this study. The personal identification number, which is issued to all residents in Sweden, was used to link data from different registers. In order to ensure anonymity, the personal identification number was replaced by a serial number by Statistics Sweden. Data from the Swedish Multi-generation register contained familial relationships data including adoptions. The Swedish National Patient register (NPR) contains data for hospital inpatients and outpatients. The Swedish cause of death register and the total population register were used. These registers contain life events including birth, death, name change, marital status, family relationships, education and migration within Sweden as well as to and from other countries.

ESRD and comorbidities

ESRD was defined among patients in NPR (1964-2012) and outpatient register (2001-2012) identified by the International classification of diseases (ICD) codes and surgical and non-surgical interventions code for chronic dialysis and kidney

transplantation (Table 4). Main and secondary diagnosis were used. Comorbidities were defined by ICD codes any time during follow-up (1964-2012).

Samples

All Swedish-born adoptees (1945 and 1995) and their biological and adoptive parents were included in the analysis. The following groups were excluded in the analysis: Adoptees who died before 16 years of age, migrated from Sweden before 16 years of age, died before 1964, or could not be linked to at least one biological and at least one adoptive parent. All adoptive children who had lived with a biological relative (parents) were excluded according to Census (1960-1990) or small area market statistics (SAMS) (from 1991).

Adoptees that had lived with their biological grandparent, aunt/uncle, and sibling or by stepparents together with their biological parent were excluded. After exclusions, a total of 37 486 adoptees remained in the study. This number constitutes the study population. The adoptees could be linked to 64139 adoptive parents and 59287 biological parents.

We identified 971 (0.59%) patients with ESRD among adoptees and their adoptive and biological parents after exclusion. These cases consisted of 111 ESRD found in adoptees, 463 ESRD cases in biological parents, and 397 ESRD in adoptive parents. Of all ESRD cases identified, 22.66% were (n= 220) found in the hospital outpatient register and 657 (67,66%) were found in the hospital discharge register through ICD codes. Moreover, we identified 4.74% (n= 46) ESRD patients through surgical codes (and non-surgical) version 6 (1963-1996), temporary non-surgical codes (1997-2006) identified 1.24% (n=12), new version of surgical codes (KVÅ, 1997-2012 and after 2007 also non-surgical codes) identified 3.71% (n=36) ESRD patients. All ESRD cases were identified with 3.50% (n=34) with ICD-8 codes, 25.85% (n=251) with ICD-9 codes and 60.97% (n=592) with ICD-10 codes.

Statistical Calculation

In study IV a cohort and case-control design was used in order to study genetic and non-genetic factors in ESRD. Two main analyses were performed: OR (odds ratio) determined with logistic regression in adoptees with an affected biological parent and in adoptees with an affected adoptive parent. Case-control matching method (1:5) by drawing a sample of ESRD affected adoptees as cases and matched control groups of ESRD unaffected adoptees (Thomas, 2004). Matching was based on gender, birth year, country of birth and level of education. In the case-control study, both groups were connected to their biological and adoptive

parents (Yates, 2011). In the case-control design OR was determined with conditional logistic regression. In the cohort design logistic regression was used to determine crude and multivariate odds ratios. Adoptees birth year, gender, education of adoptees and country of birth of adoptees were used in the multivariate model as covariates in the cohort study. In both studies, the estimated parameter was OR of ESRD in adoptees with at least one affected biological parent compared with adoptees without any affected biological parent, and similarly for adoptive parents.

Cox Regression analysis was used to compare the results between logistic regression and cox regression models. A Kaplan-Meier analysis was also provided. Competing risk of death was also considered. The estimated cumulative incidence functions (CIF) were determined for ESRD for adoptees stratified by biological parents with and without ESRD. Gray´s test was used to test the hypotheses of equality of CIF between two adoptees with and without an affected parent.

Falconer´s regression was used to evaluate the heritability of ESRD. The method is based on liability of the threshold in adoptees of biological parents according to Falconer DS, 1965 (Falconer, 1965; Falconer & Mackay, 1996). From the prevalence rate of the relatives of the biological probands and the controls (i.e. biological parents to affected and unaffected adoptees, respectively) from the case-control study, we calculated the heritability h^2 (and ± SE). Tetrachoric correlation described by Frisell (Frisell et al, 2013) was used to test the sensitivity of the calculated heritability to the assumed prevalence. Tetrachoric correlation is the inferred Pearson correlation from a 2 by 2 table with dichotomous normality being assumed. Tetrachoric correlation can vary from -1 (perfect negative correlation) through 0 (no correlation) to +1 (perfect positive correlation) in analogy to Pearson´s correlation. Tetrachoric correlation was calculated for a range of estimated population prevalence of ESRD. Assuming that only additive genetic factors contribute to the resemblance between adoptees and their biological parent relatives, heritability of liability was estimated to be twice the tetrachoric correlation among first-degree relatives (adoptees and their biological parents), (Falconer & Mackay, 1996, Frisell et al, 2013).

Statistical analysis was performed with SAS version 9.3 (SAS Institute, INC., Cary, NC, USA) and we used R software (version 3.3.2) for calculating heritability.

Chapter IV.

Statistical and epidemiological methods used

Standardised incidence ratios

Standardised incidence ratios (SIRs) were used in papers II and III, in order to measure the relative risk in individuals with one or more relative with an exposure (i.e. disease), compared with individuals without an exposure (i.e. relatives without disease). SIR is determined in a similar way to standardised mortality ratio (SMR) except that SMR is used to determine the ratio of observed deaths.

The familial SIRs were calculated as the ratio of observed (O) and expected (E) numbers of kidney failure/glomerulonephritis cases using the indirect standardisation method:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

Where $O = \sum o_j$ denotes the total observed number of cases in the study group; E^* (the expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ^*_j) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; o_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by cross-classification of the following adjustment variables: age (five-year groups), sex, socioeconomic status, time period (5-year groups), and geographic region of residence. We used 95% confidence intervals (95% CIs) to assume a Poisson distribution (Breslow & Day, 1987).

Multilevel models

Multi-level modelling was used in paper I. One solution to the problem of separating compositional (individual level)) and contextual (neighbourhood) effects is to include both individual-level and ecologic measures in the same analysis. Multilevel modelling is a statistical method that broadens ordinary regression analysis to a setting where the data are hierarchically organised. Multilevel (hierarchical) modelling is also called mixed models, random-effects models, or random parameter models. Multilevel models are statistical models of parameters that vary at more than one level. A classic example is a multilevel model of student performance that contains measures for individual students (compositional) as well as measures for classrooms (contextual). These models are generalisations of linear models, although they can also be extended to include non-linear models. These models became popular after sufficient computing power and software became available. Multilevel models are particularly appropriate for research designs where data for participants are organised at more than one level (i.e. nested data). The units of analysis are usually individuals (at a lower level) who are nested within contextual/aggregate units (at a higher level). Multilevel modelling may be used to estimate contextual and ecologic effects and to calculate improved estimates of individual-level effects. The model may also be used to estimate how much of the difference in outcome rates across groups (ecologic effect) can be explained by differences in the distribution of individual-level risk factors (biologic effects) (Greenland, 2002; Rothman et al, 2008).

Survival analysis: Cox Regression

Cox regression was used in paper IV in order to take into account the high mortality among patients with ESRD. Survival analysis is a statistical method that is designed to study time to the event of interest. The event does not need to be death, it could be, for instance, ESRD as in paper IV. Cox regression or proportional hazards model is a statistical model in survival analysis. It infers that the effect of the studied factors does not change overtime and is multiplicative (Rothman KJ, 2008; Hancock et al, 2014).

Falconer´s Regression

Falconer´s regression was used in study IV to calculate the heritability of ESRD among adoptees, with and without affected biological parents, compared with adoptees with and without an affected adoptive parent. This method is based on the liability of the threshold to obtain heritability of adoptees of biological parents (Falconer, 1965; Falconer & Mackay, 1996). In this method the prevalence rates of the relatives of the biological parents to affected and unaffected adoptees are used to calculate the heritability h^2 (and ± Standard error) according to Falconer (Falconer, 1965; Falconer & Mackay, 1996).

Gray´s test

Competing risks often occur in medical research, when studied individuals are at risk of two or more mutually exclusive events, for instance, death from different causes. The framework of competing risks also comprises settings where different potential events are not mutually exclusive but the focus is on the first presenting event. To consider the competing risk of death in paper IV, the estimated cumulative incidence functions (CIF) was determined for adoptees stratified by biological parents with and without ESRD. Equality of CIF between two adoptees with and without an affected parent was tested by Gray´s test (Gray RJ, 1988). The method makes use of the sub-distribution hazard, which is a function of the cumulative incidence for the corresponding cause of failure (Bakoyannis & Touloumi, 2012).

Chapter V.

Ethical considerations

Statistics Sweden and the National Board of Health and welfare maintain the nationwide registers used in this thesis. These studies were approved by the Ethics Committee of Lund University, Sweden (approval number 409/2008, with amendments approved on September 1 2009 and January 22 2010). Approval was performed in compliance with the Declaration of Helsinki.

Chapter VI.

Results

Population characteristics study I

The study population in study I consisted of 5,593,516 individuals (Table 4). Of the total study population 1301351 (23%), 3370070 (60%) and 922095 (17%) lived in low-, moderate-, and high deprivation neighbourhoods. During the follow-up period a total of 12,348 individuals were diagnosed with end stage renal disease (ESRD). The population characteristics of the study population and the events of ESRD are presented below in Table 4.

Table 4.
Population characteristics and end stage renal disease (ESRD) events by level of neighbourhood deprivation: 2001–2010

	Study population		**ESRD events**		**Incidence of ESRD by level of neighbourhood deprivation***		
	(N)	(%)	(N)	(%)	Low	Moderate	High
Total population	5,593,516				1301351 (23.3%)	3370070 (60.2%)	922095 (16.5%)
End Stage Renal Disease			**12,348**		1.8	2.3	2.5
Age (years)							
20-29	1,092,948	19.5	712	5.8	0.5	0.7	0.7
30-39	1,264,439	22.6	1,520	12.3	0.9	1.3	1.5
40-49	1,163,403	20.8	2,385	19.3	1.6	2.1	2.6
50-59	**1,241,349**	**22.2**	**3,950**	**32.0**	**2.6**	**3.2**	**4.0**
60-69	831,377	14.9	3,781	30.6	3.7	4.6	5.4
Sex							
Male	2,826,359	50.5	7,870	63.7	2.3	2.9	3.1
Female	2,767,157	49.5	4,478	36.3	1.3	1.6	1.9
Education level							
≤ 9 years	1,249,236	22.3	4,336	35.1	2.3	2.9	3.0
10–12 years	2,700,091	48.3	5,560	45.0	1.9	2.3	2.4
>12 years	1,644,189	29.4	2,452	19.9	1.5	1.7	1.7
Marital status							
Married/cohabiting	2,575,915	46.1	6,331	51.3	1.7	2.1	2.4
Never married, widowed, or divorced	3,017,601	53.9	6,017	48.7	1.9	2.5	2.6

Family income							
Low	1,399,791	25.0	2,781	22.5	2.0	2.5	2.8
Middle-low	1,400,677	25.0	3,489	28.3	2.2	2.6	2.8
Middle-high	1,396,660	25.0	3,348	27.1	2.0	2.3	2.5
High	1,396,388	25.0	2,730	22.1	1.5	1.9	1.8
Country of origin							
Sweden	4,797,837	85.8	10,531	85.3	1.8	2.3	2.5
Finland	163,533	2.9	379	3.1	1.5	1.9	1.8
Western countries	51,828	0.9	119	1.0	1.6	1.8	2.6
Eastern European countries	114,770	2.1	317	2.6	2.7	3.0	2.8
Middle Eastern countries	141,019	2.5	291	2.4	3.4	2.9	3.3
Others	324,529	5.8	711	5.8	1.9	2.4	2.8
Urban/rural status							
Large cities	2,854,538	51.0	6,436	52.1	1.8	2.4	2.8
Middle-sized towns	1,852,901	33.1	3,974	32.2	1.7	2.2	2.2
Small towns/rural areas	886,077	15.8	1,938	15.7	1.7	2.1	2.3
Mobility							
Not moved	3,455,429	61.8	8,912	72.2	1.8	2.3	2.5
Moved	2,138,087	38.2	3,436	27.8	1.9	2.3	2.5
Hospitalisation for chronic lower respiratory disease							
No	5,458,926	97.6	11,659	94.4	1.7	2.2	2.4
Yes	134,590	2.4	689	5.6	3.7	4.2	4.8
Hospitalisation for alcoholism and related liver disease							
No	5,475,640	97.9	11,950	96.8	1.8	2.3	2.5
Yes	117,876	2.1	398	3.2	2.5	3.5	3.0
Hospitalisation for obesity							
No	5,543,143	99.1	12,158	98.5	1.8	2.3	2.5
Yes	50,373	0.9	190	1.5	3.6	4.5	3.7
Hospitalisation for coronary heart disease							
No	5,358,377	95.8	9,307	75.4	1.5	1.8	2.0
Yes	235,139	4.2	3,041	24.6	13.9	17.3	14.6
Hospitalisation for diabetes							
No	5,426,241	97.0	8,343	67.6	1.3	1.6	1.7
Yes	167,275	3.0	4,005	32.4	19.2	23.4	22.9
Hospitalisation for hypertension							
No	5,431,660	97.1	9,502	77.0	1.5	1.8	2.0
Yes	161,856	2.9	2,846	23.0	15.5	22.1	29.0

The age-adjusted cumulative incidence rate of ESRD increased from 1.8 per 1000 neighbourhoods with low deprivation to 2.5 per 1000 in neighbourhoods with high deprivation. Men (2.3 per 1000 in low deprived neighbourhoods) and women (1.3 per 1000 in low deprived neighbourhoods) had different cumulative incidence rates of ESRD.

Neighbourhood deprivation and ESRD in men

In the crude model for men the odds ratio (OR) for ESRD living in high- versus low-deprivation neighbourhoods was 1.32 (95% confidence interval [CI] 1.22-1.43). Neighbourhood-level deprivation was significantly associated with ESRD after adjustment for age (model 2) and age plus individual-level SES variables (model 3), and in the full model (model 4) adjusted for age, individual-level SES, and comorbidities. The OR for ESRD was high for several comorbidities: 1.32 for chronic lower respiratory diseases, 2.34 for coronary heart disease, 4.92 for hypertension, and 7.62 for diabetes. Age was included as a continuous variable in models 2, 3, and 4. The OR for ESRD increased by 1.05 for every year of increasing age in models 2 and 3. After adjustment for comorbidities, the OR for age was 1.03. Male immigrants from Finland (OR=0.74) had a lower OR for ESRD than native Swedes. No other differences were observed regarding country of birth (Table 5).

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for ESRD in men; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.27	1.20	1.35	1.28	1.20	1.36	1.19	1.12	1.26	1.16	1.09	1.24	<0.001
High	1.32	1.22	1.43	1.45	1.34	1.56	1.25	1.15	1.35	1.17	1.07	1.27	<0.001
Age (years)				1.05	1.05	1.05	1.05	1.05	1.06	1.02	1.02	1.03	<0.001
Education attainment (ref. > 12 years)													
≤ 9 years							1.29	1.20	1.38	1.15	1.08	1.23	<0.001
10–12 years							1.20	1.13	1.28	1.10	1.03	1.17	0.003
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.24	1.18	1.30	1.16	1.11	1.22	<0.001
Family income (ref. High income)													
Low income							1.29	1.20	1.39	1.25	1.17	1.34	<0.001
Middle–low income							1.39	1.31	1.49	1.31	1.23	1.40	<0.001
Middle–high income							1.30	1.22	1.38	1.23	1.16	1.31	<0.001
Country of origin (ref. Sweden)													
Finland							0.82	0.72	0.94	0.74	0.65	0.85	<0.001
Western countries							0.84	0.67	1.05	0.84	0.67	1.05	0.134
Eastern European countries							1.14	0.98	1.32	1.04	0.89	1.20	0.617
Middle Eastern countries							1.09	0.94	1.27	0.95	0.82	1.11	0.549
Others							1.02	0.92	1.12	0.97	0.88	1.08	0.576
Urban/rural status (ref. Large cities)													
Middle-sized towns							0.84	0.79	0.88	0.90	0.85	0.95	<0.001
Small towns/rural areas							0.84	0.79	0.90	0.83	0.77	0.89	<0.001
Mobility (ref. Not moved)							0.99	0.94	1.05	0.94	0.89	0.99	0.024
Hospitalisation for chronic lower respiratory disease (ref. No)										1.28	1.15	1.43	<0.001
Hospitalisation for alcoholisms and related liver disease (ref. No)										0.92	0.82	1.03	0.162
Hospitalisation for coronary heart disease (ref. No)										2.31	2.18	2.44	<0.001
Hospitalisation for hypertension (ref. No)										4.83	4.56	5.11	<0.001
Hospitalisation for diabetes (ref. No)										7.32	6.95	7.70	<0.001
Hospitalisation for obesity (ref. No)										0.80	0.65	0.99	0.046
Acute kidney injury (ref. No)										9.35	8.26	10.57	<0.001
Variance (S.E.)	*0.067 (0.014)*			*0.053 (0.014)*			*0.041 (0.014)*			*0.068 (0.014)*			
Intra class correlation	0.020			0.016			0.012			0.020			

Neighbourhood deprivation and ESRD in women

Table 6 shows the different models for women. In the crude neighbourhood-level model, the OR for ESRD for women living in high- versus low-deprivation neighbourhoods was 1.51 (95% CI 1.37-1.67). Neighbourhood-level deprivation remained significantly associated with ESRD after adjustment for age (model 2) and age plus individual-level SES variables (model 3). In the full model, additionally adjusted for comorbidities, the OR was 1.18 (95% CI 1.07-1.31). Age was included as a continuous variable in models 2, 3, and 4. The OR increased by 1.04 for every year of increasing age in models 2 and 3. After inclusion of comorbidities, the OR for age was 1.02. Increased ORs for ESRD were noted in the full model (model 4) for women with low education levels or low family incomes, and for women, who were never married, widowed, or divorced. The OR was significantly decreased for women living in middle-sized or small towns/rural areas compared with those living in large cities. A slightly but significantly decreased OR was also observed for women who had moved within the previous five years. Finnish women (OR=0.66) had a lower OR for ESRD than native Swedes. Otherwise there was no association with country of birth. All included comorbidities except for obesity were significantly associated with ESRD in women. Especially high ORs were noted for diabetes (OR=9.18) and hypertension (OR=4.51), and acute kidney failure (OR=7.98) (Table 6).

Table 6. Odds ratios (OR) and 95% confidence intervals (CI) for ESRD in women; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.27	1.17	1.37	1.25	1.15	1.35	1.13	1.05	1.23	1.10	1.01	1.20	0.021
High	1.51	1.37	1.67	1.59	1.44	1.75	1.30	1.17	1.44	1.18	1.06	1.31	0.001
Age (years)				1.04	1.04	1.04	1.04	1.04	1.04	1.02	1.01	1.02	<0.001
Education attainment (ref. > 12 years)													
≤ 9 years							1.63	1.49	1.78	1.39	1.27	1.52	<0.001
10–12 years							1.35	1.24	1.46	1.25	1.15	1.35	<0.001
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.15	1.08	1.22	1.08	1.01	1.15	0.016
Family income (ref. High income)													
Low income							1.24	1.12	1.36	1.07	0.97	1.18	0.194
Middle–low income							1.39	1.27	1.52	1.17	1.06	1.28	<0.001
Middle–high income							1.20	1.09	1.31	1.10	1.00	1.20	0.046
Country of origin (ref. Sweden)													
Finland							0.76	0.65	0.89	0.66	0.56	0.78	<0.001
Western countries							0.93	0.68	1.26	0.96	0.71	1.31	0.842
Eastern European countries							1.23	1.02	1.47	1.04	0.86	1.26	0.689
Middle Eastern countries							1.06	0.86	1.31	0.88	0.71	1.08	0.230
Others							1.07	0.94	1.21	1.05	0.93	1.19	0.424
Urban/rural status (ref. Large cities)													
Middle-sized towns							0.90	0.84	0.97	0.96	0.90	1.03	0.317
Small towns/rural areas							0.87	0.79	0.95	0.86	0.78	0.94	<0.001
Mobility (ref. Not moved)							0.96	0.90	1.03	0.91	0.85	0.98	0.009
Hospitalisation for chronic lower respiratory disease (ref. No)										1.41	1.25	1.60	<0.001
Hospitalisation for alcoholisms and related liver disease (ref. No)										1.31	1.06	1.62	0.012
Hospitalisation for coronary heart disease (ref. No)										2.66	2.44	2.89	<0.001
Hospitalisation for hypertension (ref. No)										4.44	4.11	4.80	<0.001
Hospitalisation for diabetes (ref. No)										8.78	8.16	9.44	<0.001
Hospitalisation for obesity (ref. No)										0.91	0.74	1.12	0.368
Acute kidney injury (ref. No)										7.98	6.59	9.67	<0.001
Variance (S.E.)	*0.070 (0.023)*			*0.059 (0.023)*			*0.047 (0.022)*			*0.073 (0.023)*			
Intra class correlation	0.021			0.018			0.014			0.022			

Sensitivity analysis

Of all the 12348 cases with ESRD, 950 (7.7%) patients had a first diagnosis of CKD-5 without dialysis or transplantation, 4542 (36.8%) were transplant patients, and 6856 (55.5%) patients were on dialysis, Table 2. A sensitivity analysis was also performed for these three groups of ESRD patients. Men had similar OR for all three groups (Table 7). Male ESRD patients living in deprived neighbourhoods without a transplant or dialysis in the full model adjusted for age, individual variables and comorbidity the OR was 1.16 (95% CI 0.88-1.53), for ESRD patients on dialysis the OR was 1.21 (95% CI 1.07-1.35) and ESRD patients with a transplant had an OR of 1.16 (95% CI 1.03-1.30) (Table 7). Among women the highest OR was observed for ESRD patients without dialysis and transplantation OR = 1.61 (95% CI 1.12-2.31) (Table 8). The OR in the fully adjusted model for ESRD patients on dialysis was 1.15 (95% CI 1.00-1.34), and the OR for transplanted ESRD patients on dialysis was 1.22 (95% CI 1.05- 1.43) (Table 8).

Table 7.
Odds ratios (OR) and 95% confidence intervals (CI) for subtypes of end stage renal disease (ESRD) in men; Results of multi-level logistic regression models. Subanalysis according to treatment.

	ESRD (N18.5)			Dialysis			Transplantation		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighbourhood deprivation (ref. Low)									
Moderate	1.17	0.94	1.45	1.18	1.08	1.29	1.17	1.06	1.28
High	1.16	0.88	1.53	1.21	1.07	1.35	1.16	1.03	1.30
Age (years)	1.02	1.01	1.03	1.03	1.02	1.03	1.02	1.02	1.02
Education Level (ref. > 12 years)									
≤ 9 years	1.15	0.90	1.46	1.20	1.09	1.31	1.07	0.97	1.18
10–12 years	1.19	0.96	1.48	1.08	0.99	1.17	1.12	1.02	1.23
Marital status (ref. Married/cohabiting)									
Never married, Widowed, or divorced	1.07	0.90	1.27	1.09	1.02	1.17	1.23	1.14	1.32
Family income (ref. High income)									
Low income	1.30	1.01	1.67	1.23	1.12	1.36	1.24	1.11	1.37
Middle–low income	1.27	1.01	1.60	1.25	1.15	1.37	1.33	1.20	1.46
Middle–high income	1.39	1.12	1.73	1.19	1.09	1.30	1.22	1.11	1.34
Country of origin (ref. Sweden)									
Finland	0.67	0.41	1.08	0.71	0.59	0.86	0.79	0.65	0.96
Western countries	1.15	0.60	2.24	0.77	0.56	1.07	0.94	0.68	1.30
Eastern European countries	1.04	0.63	1.72	1.18	0.97	1.43	0.81	0.63	1.04
Middle Eastern countries	0.92	0.54	1.55	0.95	0.77	1.17	0.95	0.76	1.19
Others	1.05	0.75	1.46	0.96	0.83	1.11	1.00	0.86	1.16
Urban/rural status (ref. Large cities)									
Middle-sized towns	0.57	0.47	0.70	1.01	0.94	1.09	0.84	0.77	0.91
Small towns/rural areas	0.54	0.42	0.69	0.74	0.67	0.82	0.94	0.86	1.04
Mobility (ref. Not moved)	1.06	0.88	1.27	0.91	0.84	0.98	0.96	0.89	1.04
Chronic lower respiratory disease (ref. No)	1.17	0.81	1.68	1.31	1.13	1.52	1.19	1.02	1.40
Alcoholism and related liver disease (ref. No)	0.91	0.62	1.35	1.12	0.96	1.30	0.70	0.58	0.85
Coronary heart disease (ref. No)	1.95	1.61	2.37	2.17	2.01	2.35	2.42	2.23	2.63
Hypertension (ref. No)	6.94	5.80	8.32	3.67	3.38	3.98	5.69	5.25	6.16
Diabetes (ref. No)	8.26	6.93	9.86	6.40	5.96	6.89	7.89	7.32	8.50
Obesity (ref. No)	1.49	0.90	2.44	0.83	0.62	1.13	0.66	0.47	0.91
Acute kidney failure (ref. No)	15.64	11.80	20.74	5.55	4.59	6.69	9.63	8.19	11.33
Variance (S.E.)	0.415 (0.152)			0.188 (0.029)			0.075 (0.029)		

Table 8.
Odds ratios (OR) and 95% confidence intervals (CI) for subtypes of end stage renal disease (ESRD) in women; Results of multi-level logistic regression models. Subanalysis according to treatment.

	ESRD (N18.5)			Dialysis			Transplantation		
	OR	95% CI		OR	95% CI		OR	95% CI	
Neighbourhood deprivation (ref. Low)									
Moderate	1.07	0.78	1.45	1.14	1.02	1.27	1.09	0.96	1.22
High	1.61	1.12	2.31	1.15	1.00	1.34	1.22	1.05	1.43
Age (years)	1.03	1.02	1.04	1.02	1.01	1.02	1.01	1.01	1.02
Education level (ref. > 12 years)									
≤ 9 years	1.52	1.07	2.16	1.45	1.28	1.64	1.24	1.09	1.42
10–12 years	1.29	0.94	1.78	1.27	1.13	1.42	1.21	1.07	1.36
Marital status (ref. Married/cohabiting)									
Never married, Widowed, or divorced	1.26	1.00	1.59	1.08	0.99	1.17	1.02	0.93	1.12
Family income (ref. High income)									
Low income	1.43	0.97	2.09	0.96	0.84	1.09	1.10	0.95	1.28
Middle–low income	1.34	0.93	1.93	1.04	0.92	1.18	1.25	1.10	1.44
Middle–high income	1.46	1.02	2.08	1.02	0.90	1.16	1.15	1.00	1.32
Country of origin (ref. Sweden)									
Finland	0.92	0.56	1.52	0.63	0.50	0.80	0.65	0.51	0.83
Western countries	0.28	0.04	2.03	1.22	0.84	1.78	0.77	0.46	1.29
Eastern European countries	1.20	0.67	2.16	1.05	0.81	1.36	0.94	0.71	1.26
Middle Eastern countries	0.71	0.34	1.49	1.07	0.81	1.41	0.69	0.49	0.97
Others	0.88	0.56	1.40	1.11	0.94	1.32	0.99	0.82	1.20
Urban/rural status (ref. Large cities)									
Middle-sized towns	0.50	0.38	0.66	1.04	0.95	1.15	0.93	0.84	1.04
Small towns/rural areas	0.49	0.34	0.70	0.82	0.72	0.93	0.95	0.84	1.08
Mobility (ref. Not moved)	1.10	0.85	1.42	0.87	0.79	0.96	0.95	0.85	1.05
Chronic lower respiratory disease (ref. No)	1.72	1.17	2.54	1.38	1.16	1.63	1.42	1.19	1.70
Alcoholism and related liver disease (ref. No)	1.34	0.66	2.72	1.53	1.16	2.01	0.96	0.67	1.37
Coronary heart disease (ref. No)	2.10	1.55	2.86	2.52	2.24	2.84	2.91	2.57	3.30
Hypertension (ref. No)	5.56	4.24	7.29	3.76	3.36	4.20	4.88	4.35	5.47
Diabetes (ref. No)	8.18	6.27	10.68	7.90	7.14	8.75	9.62	8.64	10.72
Obesity (ref. No)	0.94	0.46	1.92	0.91	0.68	1.23	0.89	0.66	1.21
Acute kidney failure (ref. No)	15.52	9.95	24.21	5.52	4.16	7.34	7.74	5.96	10.04
Variance (S.E.)	0.172 (0.251)			0.188 (0.029)			0.075 (0.029)		

The aetiology of ESRD is heterogeneous. In paper I the multilevel modelling was also done with exclusion of patients with the following diagnoses: cystic kidney disease (ICD-10 Q61), congenital kidney and urinary tract malformations (Q60, Q62, Q63, Q64), urolithiasis (N20-N23), rare inherited kidney diseases such as Alport's syndrome and Laurence–Moon–Biedl–Bardet syndrome (Q87.8A, Q87.8B), hyper- oxaluria (E74.8B), glomerular disease (N00-N08), and tubular

interstitial diseases (N10-N16). A total of 3.1% (n = 172055) of the total study population (5593516) was excluded. Among ESRD cases, these diagnoses constituted 46% (n = 5691) of all 12348 ESRD patients. The association between neighbourhood deprivation and ESRD became even stronger for both women and men after the exclusions (Tables 9 and 10). In the fully adjusted model 4, the OR in highly deprived neighbourhoods was 1.33 (95% CI 1.1.19–1.49) for men and 1.31 (95% CI 1.13–1.51) for women (Tables 9 and 10).

Table 9. (OR) and 95% confidence intervals (CI) for end stage renal disease ESRD in men; Results of multi-level logistic regression models after exclusions*

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.37	1.26	1.50	1.37	1.26	1.50	1.29	1.19	1.41	1.26	1.15	1.37	<0.001
High	1.52	1.37	1.68	1.68	1.51	1.86	1.44	1.29	1.61	1.33	1.19	1.49	<0.001
Age (years)				1.06	1.06	1.06	1.07	1.06	1.07	1.03	1.03	1.04	<0.001
Education attainment (ref. > 12 years)													
≤ 9 years							1.37	1.25	1.50	1.21	1.10	1.33	<0.001
10–12 years							1.25	1.15	1.37	1.13	1.04	1.24	0.004
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.24	1.17	1.32	1.15	1.07	1.22	<0.001
Family income (ref. High income)													
Low income							1.29	1.18	1.42	1.24	1.12	1.36	<0.001
Middle–low income							1.44	1.32	1.57	1.32	1.21	1.44	<0.001
Middle–high income							1.28	1.18	1.39	1.20	1.10	1.31	<0.001
Country of origin (ref. Sweden)													
Finland							0.86	0.72	1.02	0.76	0.64	0.91	0.003
Western countries							0.85	0.64	1.15	0.86	0.64	1.15	0.317
Eastern European countries							0.98	0.80	1.21	0.90	0.73	1.11	0.317
Middle Eastern countries							1.17	0.96	1.42	0.99	0.81	1.21	0.920
Others							0.99	0.86	1.13	0.95	0.82	1.08	0.424
Urban/rural status (ref. Large cities)													
Middle-sized towns							0.74	0.69	0.79	0.80	0.75	0.86	<0.001
Small towns/rural areas							0.74	0.67	0.81	0.73	0.67	0.80	<0.001
Mobility (ref. Not moved)							1.01	0.94	1.09	0.95	0.88	1.02	0.162
Hospitalisation for chronic lower respiratory disease (ref. No)										1.34	1.16	1.53	<0.001
Hospitalisation for alcoholism and related liver disease (ref. No)										1.13	0.98	1.30	0.089
Hospitalisation for coronary heart disease (ref. No)										2.25	2.10	2.42	<0.001
Hospitalisation for hypertension (ref. No)										4.41	4.10	4.76	<0.001
Hospitalisation for diabetes (ref. No)										9.23	8.64	9.87	<0.001
Hospitalisation for obesity (ref. No)										0.73	0.55	0.98	0.036
Hospitalisation for acute kidney injury (ref. No)										8.65	7.35	10.18	<0.001
Variance (S.E.)	*0.132 (0.026)*			*0.119 (0.026)*			*0.094 (0.025)*			*0.136 (0.026)*			

Table 10. (OR) and 95% confidence intervals (CI) for end stage renal disease ESRD in women; Results of multi-level logistic regression models after exclusions*

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.37	1.22	1.53	1.34	1.19	1.49	1.22	1.09	1.37	1.18	1.05	1.33	0.004
High	1.67	1.46	1.92	1.75	1.53	2.01	1.45	1.26	1.68	1.31	1.13	1.51	<0.001
Age (years)				1.05	1.05	1.06	1.05	1.05	1.06	1.03	1.02	1.03	<0.001
Education level (ref. > 12 years)													
≤ 9 years							1.67	1.47	1.89	1.40	1.24	1.60	<0.001
10–12 years							1.32	1.17	1.47	1.20	1.07	1.35	0.002
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.20	1.10	1.31	1.12	1.03	1.23	0.007
Family income (ref. High income)													
Low income							1.31	1.14	1.50	1.11	0.96	1.27	0.162
Middle–low income							1.44	1.27	1.63	1.19	1.05	1.35	0.007
Middle–high income							1.18	1.04	1.34	1.07	0.94	1.22	0.317
Country of origin (ref. Sweden)													
Finland							0.70	0.56	0.88	0.61	0.48	0.76	<0.001
Western countries							0.84	0.54	1.29	0.86	0.55	1.32	0.484
Eastern European countries							0.91	0.68	1.21	0.76	0.56	1.01	0.057
Middle Eastern countries							0.90	0.65	1.23	0.71	0.52	0.97	0.036
Others							0.97	0.82	1.16	0.95	0.80	1.14	0.617
Urban/rural status (ref. Large cities)													
Middle-sized towns							0.80	0.72	0.88	0.85	0.77	0.93	0.001
Small towns/rural areas							0.79	0.69	0.89	0.78	0.69	0.89	<0.001
Mobility (ref. Not moved)							0.99	0.90	1.10	0.93	0.84	1.03	0.162
Chronic lower respiratory disease (ref. No)										1.36	1.15	1.60	<0.001
Alcoholism and related liver disease (ref. No)										1.86	1.46	2.39	<0.001
Coronary heart disease (ref. No)										2.91	2.60	3.26	<0.001
Hypertension (ref. No)										3.74	3.35	4.17	<0.001
Diabetes (ref. No)										10.28	9.32	11.34	<0.001
Obesity (ref. No)										0.81	0.60	1.11	0.194
Acute kidney failure (ref. No)										7.13	5.49	9.25	<0.001
Variance (S.E.)	*0.138 (0.045)*			*0.121 (0.045)*			*0.101 (0.045)*			*0.146 (0.045)*			

Intraclass correlation (ICC)

The intraclass correlation (ICC), which reflects the contribution of the contextual level (neighbourhood) to the total variance, was calculated for each model in the analysis of multilevel logistic regression. In the full model, which was adjusted for the individual level sociodemographic variables and comorbidities, the ICC was 2.0% for men and 2.2% for women (Table 5 and 6). These numbers were not presented in the published paper but are now shown in Table 5 and 6).

Multilevel analysis of ESRD treated with chronic dialysis or kidney transplantation

In paper IV a more severe phenotype of ESRD was defined by treatment of chronic dialysis or kidney transplantation. This severe phenotype of ESRD was used for recalculation of the multilevel analysis in paper I (Table 11 and Table 12). There was no major difference in ORs. The OR was only slightly higher (OR=1.20 for men and OR=1.28 for women) (Tables 11 and 12) compared to the definition used in published paper I. The ICCs were also slightly higher - 3.7% for men and 6.7% for women, respectively. Thus, neighbourhood deprivation (contextual level) contributed slightly more to the total variance when a more severe phenotype was defined.

Table 11(OR) and 95% confidence intervals (CI) for dialysed or transplanted ESRD in men; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.32	1.24	1.40	1.32	1.24	1.40	1.19	1.12	1.27	1.17	1.10	1.25	<0.001
High	1.38	1.28	1.49	1.51	1.40	1.63	1.28	1.18	1.38	1.20	1.11	1.30	<0.001
Age (years)				1.05	1.05	1.06	1.06	1.05	1.06	1.03	1.03	1.03	<0.001
Education attainment (ref. ≥ 12 years)													
≤ 9 years							1.30	1.22	1.39	1.17	1.10	1.25	0.976
10–11 years							1.21	1.14	1.28	1.11	1.04	1.18	<0.001
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.25	1.19	1.30	1.17	1.12	1.23	<0.001
Family income (ref. High income)													
Low income							1.33	1.24	1.42	1.28	1.20	1.37	<0.001
Middle–low income							1.43	1.35	1.53	1.34	1.26	1.43	<0.001
Middle–high income							1.32	1.24	1.40	1.26	1.18	1.33	<0.001
Country of origin (ref. Sweden)													
Finland							0.77	0.68	0.88	0.69	0.61	0.79	<0.001
Western countries							0.76	0.60	0.95	0.76	0.60	0.95	0.089
Eastern European countries							1.09	0.94	1.26	1.00	0.86	1.16	0.842
Middle Eastern countries							1.06	0.92	1.23	0.93	0.80	1.08	0.230
Others							0.99	0.89	1.09	0.95	0.86	1.05	0.347
Urban/rural status (ref. Large cities)													
Middle-sized towns							0.97	0.93	1.02	1.05	1.00	1.11	<0.001
Small towns/rural areas							0.88	0.82	0.94	0.86	0.81	0.93	<0.001
Mobility (ref. not moved)							1.00	0.95	1.05	0.95	0.90	0.99	<0.001
Hospitalisation for chronic lower respiratory disease (ref. No)										1.36	1.23	1.51	<0.001
Hospitalisation for alcoholisms and related liver disease (ref. No)										1.05	0.94	1.17	0.549
Hospitalisation for coronary heart disease (ref. No)										2.33	2.21	2.46	<0.001
Hospitalisation for hypertension (ref. No)										4.57	4.33	4.83	0.317
Hospitalisation for diabetes (ref. No)										6.96	6.63	7.31	<0.001
Hospitalisation for obesity (ref. No)										0.82	0.66	1.00	0.072
Acute kidney failure (ref. No)										7.26	6.38	8.26	0.072
Variance (S.E.)	*0.124 (0.015)*			*0.102 (0.014)*			*0.094 (0.014)*			*0.128 (0.015)*			
Intra class correlation	0.036			0.030			0.028			0.037			

Table 12.
Odds ratios (OR) and 95% confidence intervals (CI) for dialysed or transplanted ESRD in women; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			Model 4			
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighbourhood deprivation (ref. Low)													
Moderate	1.35	1.24	1.46	1.33	1.22	1.44	1.17	1.08	1.27	1.14	1.05	1.24	0.005
High	1.66	1.50	1.83	1.72	1.56	1.90	1.40	1.26	1.55	1.28	1.15	1.43	<0.001
Age (years)				1.04	1.04	1.04	1.04	1.04	1.04	1.02	1.02	1.02	<0.001
Education attainment (ref. ≥ 12 years)													
≤ 9 years							1.61	1.48	1.75	1.39	1.27	1.51	0.005
10–11 years							1.32	1.23	1.43	1.23	1.14	1.33	<0.001
Marital status (ref. Married/cohabiting)													
Never married, Widowed, or divorced							1.16	1.09	1.22	1.09	1.03	1.15	0.021
Family income (ref. High income)													
Low income							1.25	1.14	1.37	1.08	0.98	1.18	0.012
Middle–low income							1.39	1.28	1.51	1.18	1.08	1.28	<0.001
Middle–high income							1.19	1.10	1.30	1.10	1.01	1.20	0.005
Country of origin (ref. Sweden)													
Finland							0.72	0.62	0.85	0.64	0.55	0.75	<0.001
Western countries							0.97	0.73	1.28	1.00	0.76	1.33	0.689
Eastern European countries							1.18	0.99	1.40	1.02	0.85	1.21	0.842
Middle Eastern countries							1.02	0.84	1.25	0.86	0.70	1.05	0.134
Others							0.98	0.87	1.11	0.97	0.86	1.09	0.529
Urban/rural status (ref. Large cities)													
Middle-sized towns							1.12	1.05	1.20	1.20	1.12	1.29	0.390
Small towns/rural areas							0.89	0.81	0.97	0.88	0.80	0.97	0.002
Mobility (ref. not moved)							1.01	0.94	1.08	0.95	0.89	1.02	0.021
Hospitalisation for chronic lower respiratory disease (ref. No)										1.51	1.35	1.68	<0.001

Hospitalisation for alcoholisms and related liver disease (ref. No)										1.41	1.17	1.71	0.005
Hospitalisation for coronary heart disease (ref. No)										2.74	2.53	2.97	<0.001
Hospitalisation for hypertension (ref. No)										4.02	3.72	4.34	<0.001
Hospitalisation for diabetes (ref. No)										8.31	7.76	8.90	<0.001
Hospitalisation for obesity (ref. No)										0.96	0.79	1.16	0.484
Acute kidney failure (ref. No)										6.46	5.28	7.91	0.072
Variance (S.E.)	*0.257 (0.026)*			*0.235 (0.025)*			*0.206 (0.025)*			*0.237 (0.025)*			
Intra class correlation	0.072			0.067			0.059			0.067			

Population characteristics Study II

In study II we analysed familial risks of kidney failure in siblings/offspring in a nationwide setting. Individuals diagnosed with kidney failure aged 0-78 years between 1987-2010 were included (Table 13). A total of 8054071 individuals were included in this cohort. A total of 32462 patients were diagnosed with kidney failure: 20688 (64%) males and 11774 (36%) females (Table 13). Of the patients diagnosed with kidney failure, 10063 (31%) had acute kidney failure, 18668 (57.5 %) had chronic kidney failure, and 3731 (11.5%) had unspecified kidney failure (not specified as acute or chronic). Comorbidities were common among patients with kidney failure. Lower incidence rates were observed among children while higher incidence rates were observed among older people. The characteristics of the study population are presented in Table 13.

Table 13.
Study population and number of kidney failure events during follow up (1987-2010) in individuals aged 0 to 78 years (born 1932 and later and alive in 1987)

	Males				Females				All			
	Population		Kidney failure events		Population		Kidney failure events		Population		Kidney failure events	
	No	%	No	%	No	%	No	%	No	%	No	%
Age at diagnosis (years)												
0-9			286	1.4			263	2.2			549	1.7
10-19			424	2.0			419	3.6			843	2.6
20-29			998	4.8			706	6.0			1704	5.2
30-39			1695	8.2			1100	9.3			2795	8.6
40-49			2698	13.0			1585	13.5			4283	13.2
50-59			4712	22.8			2557	21.7			7269	22.4
60-69			6700	32.4			3477	29.5			10177	31.4
70-78			3175	15.3			1667	14.2			4842	14.9
Subtype of kidney failure												
Acute kidney failure			6385	30.9			3678	31.2			10063	31.0
Chronic kidney failure			11872	57.4			6796	57.7			18668	57.5
Unspecified kidney failure			2431	11.7			1300	11.1			3731	11.5
Socioeconomic status												
Farmer	69645	1.7	609	2.9	50935	1.3	263	2.2	120580	1.5	872	2.7
Self-employed	161705	3.9	1591	7.7	106967	2.7	476	4.0	268672	3.3	2067	6.4
Professional	359536	8.7	2435	11.8	251700	6.4	720	6.1	611236	7.6	3155	9.7
White-collar worker	1192177	29.0	5898	28.5	1390397	35.3	4421	37.5	2582574	32.1	10319	31.8
Blue-collar worker	1848695	45.0	9952	48.1	1689070	42.8	5750	48.8	3537765	43.9	15702	48.4
Other	480443	11.7	203	1.0	452801	11.5	144	1.2	933244	11.6	347	1.1
Region of residence												
Northern Sweden	427832	10.4	2120	10.2	402535	10.2	1290	11.0	830367	10.3	3410	10.5
Large city	1632588	39.7	8828	42.7	1575746	40.0	4861	41.3	3208334	39.8	13689	42.2
Southern Sweden	2051781	49.9	9740	47.1	1963589	49.8	5623	47.8	4015370	49.9	15363	47.3
Chronic obstructive pulmonary disease												
No	3910183	95.1	18979	91.7	3763810	95.5	10467	88.9	7673993	95.3	29446	90.7
Yes	202018	4.9	1709	8.3	178060	4.5	1307	11.1	380078	4.7	3016	9.3
Obesity												
No	4080976	99.2	20058	97.0	3885685	98.6	11217	95.3	7966661	98.9	31275	96.3
Yes	31225	0.8	630	3.0	56185	1.4	557	4.7	87410	1.1	1187	3.7

Alcoholism and related liver disease												
No	3994406	97.1	18453	89.2	3883021	98.5	11184	95.0	7877427	97.8	29637	91.3
Yes	117795	2.9	2235	10.8	58849	1.5	590	5.0	176644	2.2	2825	8.7
Diabetes Mellitus												
No	3998103	97.2	13930	67.3	3868649	98.1	8345	70.9	7866752	97.7	22275	68.6
Yes	114098	2.8	6758	32.7	73221	1.9	3429	29.1	187319	2.3	10187	31.4
Hyptertension												
No	3928928	95.5	10841	52.4	3791314	96.2	6965	59.2	7720242	95.9	17806	54.9
Yes	183273	4.5	9847	47.6	150556	3.8	4809	40.8	333829	4.1	14656	45.1
Coronary heart disease												
No	3975828	96.7	15160	73.3	3879307	98.4	9561	81.2	7855135	97.5	24721	76.2
Yes	136373	3.3	5528	26.7	62563	1.6	2213	18.8	198936	2.5	7741	23.8
Stroke												
No	4038432	98.2	17537	84.8	3892316	98.7	10276	87.3	7930748	98.5	27813	85.7
Yes	73769	1.8	3151	15.2	49554	1.3	1498	12.7	123323	1.5	4649	14.3
Hyperlipidaemia												
No	4067712	98.9	19437	94.0	3917158	99.4	11233	95.4	7984870	99.1	30670	94.5
Yes	44489	1.1	1251	6.0	24712	0.6	541	4.6	69201	0.9	1792	5.5
Heart failure												
No	4068915	98.9	16408	79.3	3920737	99.5	9833	83.5	7989652	99.2	26241	80.8
Yes	43286	1.1	4280	20.7	21133	0.5	1941	16.5	64419	0.8	6221	19.2
All	4112201	100.0	20688	100.0	3941870	100.0	11774	100.0	8054071	100.0	32462	100.0

Kidney failure and familial risks

Familial risks of kidney failure according to disease subtypes are presented in Table 14. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Concordant (same disease in proband and relative) and discordant (different disease in proband and relative) risks were determined. The familial risks were highest for chronic kidney failure: the concordant familial SIR for chronic kidney failure was 2.02. The concordant familial risk was not significantly increased for acute kidney failure (SIR=1.08) and for unspecified kidney failure (SIR=1.25) (Table 14). However, discordant risks show that family history (sibling/parent) of chronic kidney failure is a risk factor for both acute kidney failure (SIR=1.19) and unspecific kidney failure (SIR=1.63) (Table 14). Moreover, discordant risks show that family history (sibling/parent) of acute kidney failure is a risk factor for both chronic kidney failure (SIR=1.10) and unspecific kidney failure (SIR=1.30) (Table 14). Family history of unspecified kidney failure (sibling/parent) was a risk factor for chronic kidney failure (SIR=1.31) (Table 14). Family history of all kidney failure was a risk factor for all types of kidney failure (Table 14). Familial risks of kidney failure were determined in both males and females. There were no major sex differences (Table 14).

Table 14.
Familial concordant and discordant risk (sibling/parent history) of kidney failure in males and females

		Males				Females				All			
Type of kidney failure in proband	Subtype of kidney failure in offspring/sibling	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Acute kidney failure	Acute kidney failure	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure	282	1.07	0.95	1.20	153	1.15	0.98	1.35	435	1.10	1.00	1.21
	Unspecified kidney failure	64	1.29	1.00	1.65	36	1.31	0.92	1.81	100	1.30	1.06	1.58
	All kidney failure	499	1.10	1.01	1.20	273	1.14	1.01	1.28	772	1.11	1.04	1.19
Chronic kidney failure	Acute kidney failure	201	1.15	0.99	1.32	129	1.26	1.05	1.50	330	1.19	1.06	1.32
	Chronic kidney failure	717	2.04	1.90	2.20	395	1.97	1.78	2.17	1112	2.02	1.90	2.14
	Unspecified kidney failure	104	1.56	1.28	1.89	65	1.76	1.36	2.24	169	1.63	1.40	1.90
	All kidney failure	1022	1.72	1.62	1.83	589	1.73	1.59	1.88	1611	1.73	1.64	1.81
Unspecified kidney failure	Acute kidney failure	72	1.07	0.84	1.35	42	1.04	0.75	1.41	114	1.06	0.88	1.28
	Chronic kidney failure	176	1.31	1.12	1.52	101	1.31	1.07	1.60	277	1.31	1.16	1.47
	Unspecified kidney failure	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
	All kidney failure	281	1.22	1.09	1.38	164	1.24	1.06	1.44	445	1.23	1.12	1.35
All kidney failure	Acute kidney failure	426	1.11	1.01	1.22	255	1.15	1.01	1.30	681	1.12	1.04	1.21
	Chronic kidney failure	1175	1.57	1.48	1.66	649	1.58	1.46	1.71	1824	1.57	1.50	1.65
	Unspecified kidney failure	201	1.39	1.21	1.60	122	1.53	1.27	1.83	323	1.44	1.29	1.61
	All kidney failure	1802	1.41	1.35	1.48	1026	1.44	1.35	1.53	2828	1.42	1.37	1.48

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00.
O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Table 15.
Familial risk of concordant kidney failure in males and females for different types of relatives.

		Males				Females				All			
Probands with any type of kidney failure	Subtype of kidney failure in offspring/siblings	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Family history (parent/sibling)	Acute kidney failure	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure	717	2.04	1.90	2.20	395	1.97	1.78	2.17	1112	2.02	1.90	2.14
	Unspecified kidney failure	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
	All kidney failure	1802	1.41	1.35	1.48	1026	1.44	1.35	1.53	2828	1.42	1.37	1.48
Parents history	Acute kidney failure	103	1.06	0.87	1.29	58	1.10	0.83	1.42	161	1.07	0.91	1.25
	Chronic kidney failure	378	1.71	1.54	1.89	204	1.62	1.40	1.85	582	1.67	1.54	1.82
	Unspecified kidney failure	22	1.00	0.63	1.52	16	1.50	0.86	2.45	38	1.16	0.82	1.60
	All kidney failure	1124	1.28	1.21	1.36	637	1.32	1.22	1.43	1761	1.29	1.23	1.35
Paternal history	Acute kidney failure	62	1.20	0.92	1.54	26	1.03	0.67	1.51	88	1.14	0.92	1.41
	Chronic kidney failure	212	1.73	1.50	1.98	105	1.45	1.19	1.76	317	1.62	1.45	1.81
	Unspecified kidney failure	9	0.74	0.33	1.40	11	1.87	0.93	3.36	20	1.10	0.67	1.71
	All kidney failure	637	1.35	1.24	1.45	326	1.21	1.08	1.35	963	1.29	1.21	1.38
Maternal history	Acute kidney failure	42	0.92	0.66	1.25	33	1.19	0.82	1.67	75	1.02	0.80	1.28
	Chronic kidney failure	178	1.69	1.45	1.96	108	1.88	1.54	2.27	286	1.76	1.56	1.97
	Unspecified kidney failure	13	1.26	0.67	2.16	7	1.39	0.55	2.89	20	1.31	0.80	2.02
	All kidney failure	513	1.20	1.10	1.31	326	1.47	1.31	1.63	839	1.29	1.21	1.38
Sibling history	Acute kidney failure	52	1.15	0.86	1.50	27	0.98	0.64	1.43	79	1.08	0.86	1.35
	Chronic kidney failure	366	2.52	2.27	2.80	213	2.52	2.19	2.88	579	2.52	2.32	2.73
	Unspecified kidney failure	12	1.65	0.85	2.89	6	1.08	0.39	2.37	18	1.40	0.83	2.22
	All kidney failure	738	1.68	1.56	1.80	430	1.70	1.54	1.87	1168	1.69	1.59	1.78

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00.
O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

In Table 15, familial concordant risks are presented according to type of affected relative. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Sibling history of chronic kidney failure showed the highest familial risk, with a concordant SIR of 2.52 (95% CI 2.32 - 2.73). The familial concordant risk for individuals with a parental history of chronic kidney failure was 1.67. There were no major sex differences. The familial concordant risks for acute and unspecified kidney failure were not significant (Table 15).

The familial concordant risks (parent/sibling history) were stratified according to age at diagnosis (Table 16). The familial risks for chronic kidney failure were highly age dependent and highest risks were observed at younger ages (SIR=6.33 between the age of 10 and 19 years). Increased concordant familial risk of 1.81 was noted also for chronic kidney failure for those aged 60 years or more (Table 16). The familial concordant risks for chronic kidney failure were increased in all age groups except those younger than 10 years. For acute kidney failure, the familial concordant risks were only significantly increased in two age groups (Table 16). The familial risk for acute kidney failure before age of 10 years was high (SIR=14.21). The ages of these six children with familial acute kidney failure were 0, 1, 1, 5, 5, and 7 years, respectively. For three children, the diagnosis was unknown (two had ICD diagnosis = Z038 and one had no additional diagnosis). One child was prematurely born (<28 weeks) and/or had a very low birth weight (<1000g) (ICD-9=765A), one had unspecified infectious gastroenteritis (ICD-9=009B), and one had gastroenteritis with Escherichia coli (ICD-9=008A). No significantly increased risk for unspecified kidney failure was observed for any other age groups. However, the familial risk for all kidney failure was increased in all age groups (Table 16).

Table 16.
Familial risk (sibling/parent history) of concordant kidney failure in males and females by age at diagnosis

	Males				Females				All			
Age at diagnosis (years)	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Acute kidney failure												
<10	4	16.78	4.36	43.39	2	10.88	1.03	40.02	6	14.21	5.11	31.14
10-19	0				0				0			
20-29	6	2.00	0.72	4.37	5	3.70	1.17	8.70	11	2.52	1.25	4.53
30-39	11	1.43	0.71	2.57	2	0.61	0.06	2.24	13	1.18	0.63	2.03
40-49	22	1.23	0.77	1.87	14	1.57	0.86	2.64	36	1.34	0.94	1.86
50-59	52	1.35	1.01	1.78	21	0.84	0.52	1.28	73	1.15	0.90	1.45
>=60	58	0.80	0.61	1.03	40	0.99	0.71	1.35	98	0.87	0.70	1.06
All	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
Chronic kidney failure												
<10	2	3.92	0.37	14.41	0				2	2.09	0.20	7.70
10-19	16	6.94	3.96	11.30	11	5.60	2.78	10.06	27	6.33	4.16	9.22
20-29	41	4.87	3.49	6.61	33	4.35	2.99	6.12	74	4.62	3.63	5.81
30-39	91	2.36	1.90	2.90	43	1.76	1.27	2.37	134	2.13	1.78	2.52
40-49	135	2.08	1.75	2.47	75	2.11	1.66	2.65	210	2.09	1.82	2.40
50-59	187	1.86	1.60	2.14	92	1.74	1.40	2.14	279	1.82	1.61	2.04
>=60	245	1.81	1.59	2.05	141	1.81	1.52	2.14	386	1.81	1.63	2.00
All	717	2.04	1.90	2.20	395	1.97	1.78	2.17	1112	2.02	1.90	2.14
Unspecified kidney failure												
<10	0				0				0			
10-19	0				0				0			
20-29	1	2.39	0.00	13.67	1	4.41	0.00	25.26	2	3.10	0.29	11.38
30-39	6	2.80	1.01	6.12	1	1.04	0.00	5.95	7	2.25	0.89	4.66
40-49	2	0.58	0.05	2.12	4	1.62	0.42	4.18	6	1.01	0.36	2.21
50-59	8	1.04	0.45	2.07	4	1.18	0.31	3.05	12	1.09	0.56	1.90

>=60	16	1.13	0.64	1.83	11	1.35	0.67	2.43	27	1.21	0.80	1.76
All	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
All kidney failure												
<10	6	3.28	1.18	7.19	6	3.52	1.27	7.71	12	3.40	1.75	5.95
10-19	23	3.43	2.17	5.15	24	4.02	2.57	5.98	47	3.70	2.72	4.93
20-29	72	2.53	1.98	3.18	56	2.83	2.14	3.68	128	2.65	2.21	3.15
30-39	180	1.74	1.49	2.01	87	1.47	1.18	1.82	267	1.64	1.45	1.85
40-49	290	1.45	1.29	1.63	178	1.58	1.36	1.83	468	1.50	1.37	1.64
50-59	515	1.41	1.29	1.54	260	1.30	1.15	1.47	775	1.37	1.28	1.47
>=60	716	1.25	1.16	1.35	415	1.32	1.20	1.46	1131	1.28	1.20	1.35
All	1802	1.41	1.35	1.48	1026	1.44	1.35	1.53	2828	1.42	1.37	1.48

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00. O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Test for the extent of the shared non-genetic familial contribution

In order to test for the extent of environmental sharing in the observed risks of kidney failure, we calculated the SIRs for siblings according to difference in age. (Table 17). In the model we adjusted the familial risks for age, sex, time period, region of residence, socioeconomic status, and comorbidities. The age difference had little effect. Siblings with an age difference of <5 years showed an SIR for all kidney failure of 1.64 (95% CI, 1.50 to 1.79) compared with 1.72 (95% CI, 1.59 to 1.86) for those with an age difference of ≥5 years. The concordant sibling risk for chronic kidney failure was 2.36 (95% CI 2.07-2.67) for siblings with an age difference of <5 years, compared with 2.65 (95% CI, 2.38 to 2.95) for those with an age difference of ≥5 years.

Table 17.
Familial risk of concordant kidney failure among siblings by age difference in siblings

	Age difference < 5 years				**Age difference ≥ 5 years**			
Subtype of kidney failure in siblings	O	SIR	95% CI		O	SIR	95% CI	
Acute kidney failure	34	1.26	0.87	1.77	45	0.98	0.71	1.31
Chronic kidney failure	242	2.36	2.07	2.67	337	2.65	2.38	2.95
Unspecified kidney failure	10	2.30	1.09	4.24	8	0.94	0.40	1.87
All kidney failure	516	1.64	1.50	1.79	652	1.72	1.59	1.86

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Bold type: 95% CI does not include 1.00. O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Additional analyses

Table 18 presents the familial concordant and discordant risks according to the affected relative. We adjusted the familial risks for age, sex, time period, region of residence, socioeconomic status, and comorbidities. The results were basically similar to the familial concordant/discordant risk in Table 15. Thus, concordant and discordant risk was generally highest for chronic kidney failure, followed by unspecified kidney failure, and weakest for acute kidney failure independent of the type of affected relative (sibling/parent, parents, mother, father or sibling).

Table 18.
Familial risk of concordant and discordant kidney failure in men and women according to type of kidney failure in affected relative.

		Males				Females				All			
Probands with any type of kidney failure	Subtype of kidney failure in offspring/siblings	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Family history (parent/sibling)													
Acute kidney failure	Acute kidney failure	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure	282	1.07	0.95	1.20	153	1.15	0.98	1.35	435	1.10	1.00	1.21
	Unspecified kidney failure	64	1.29	1.00	1.65	36	1.31	0.92	1.81	100	1.30	1.06	1.58
	All kidney failure	499	1.10	1.01	1.20	273	1.14	1.01	1.28	772	1.11	1.04	1.19
Chronic kidney failure	Acute kidney failure	201	1.15	0.99	1.32	129	1.26	1.05	1.50	330	1.19	1.06	1.32
	Chronic kidney failure	717	2.04	1.90	2.20	395	1.97	1.78	2.17	1112	2.02	1.90	2.14
	Unspecified kidney failure	104	1.56	1.28	1.89	65	1.76	1.36	2.24	169	1.63	1.40	1.90
	All kidney failure	1022	1.72	1.62	1.83	589	1.73	1.59	1.88	1611	1.73	1.64	1.81
Unspecified kidney failure	Acute kidney failure	72	1.07	0.84	1.35	42	1.04	0.75	1.41	114	1.06	0.88	1.28
	Chronic kidney failure	176	1.31	1.12	1.52	101	1.31	1.07	1.60	277	1.31	1.16	1.47
	Unspecified kidney failure	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
	All kidney failure	281	1.22	1.09	1.38	164	1.24	1.06	1.44	445	1.23	1.12	1.35
All kidney failure	Acute kidney failure	426	1.11	1.01	1.22	255	1.15	1.01	1.30	681	1.12	1.04	1.21
	Chronic kidney failure	1175	1.57	1.48	1.66	649	1.58	1.46	1.71	1824	1.57	1.50	1.65
	Unspecified kidney failure	201	1.39	1.21	1.60	122	1.53	1.27	1.83	323	1.44	1.29	1.61
	All kidney failure	1802	1.41	1.35	1.48	1026	1.44	1.35	1.53	2828	1.42	1.37	1.48
Parents history													
Acute kidney failure	Acute kidney failure	103	1.06	0.87	1.29	58	1.10	0.83	1.42	161	1.07	0.91	1.25
	Chronic kidney failure	189	1.01	0.87	1.17	112	1.16	0.95	1.39	301	1.06	0.95	1.19
	Unspecified kidney failure	49	1.37	1.01	1.81	24	1.23	0.79	1.83	73	1.32	1.03	1.66
	All kidney failure	341	1.07	0.96	1.19	194	1.15	0.99	1.32	535	1.10	1.00	1.19
Chronic kidney failure	Acute kidney failure	118	1.07	0.89	1.28	84	1.40	1.12	1.73	202	1.19	1.03	1.36
	Chronic kidney failure	378	1.71	1.54	1.89	204	1.62	1.40	1.85	582	1.67	1.54	1.82
	Unspecified kidney failure	68	1.72	1.33	2.18	31	1.37	0.93	1.95	99	1.59	1.29	1.94
	All kidney failure	564	1.52	1.40	1.65	319	1.53	1.36	1.71	883	1.52	1.42	1.63

Unspecified kidney failure	Acute kidney failure	59	1.09	0.83	1.40		32	1.01	0.69	1.43		91	1.06	0.85	1.30
	Chronic kidney failure	138	1.23	1.03	1.45		76	1.21	0.96	1.52		214	1.22	1.06	1.40
	Unspecified kidney failure	22	1.00	0.63	1.52		16	1.50	0.86	2.45		38	1.16	0.82	1.60
	All kidney failure	219	1.16	1.01	1.32		124	1.18	0.98	1.41		343	1.17	1.05	1.30
All kidney failure	Acute kidney failure	280	1.07	0.95	1.20		174	1.20	1.03	1.40		454	1.12	1.02	1.23
	Chronic kidney failure	705	1.36	1.26	1.46		392	1.37	1.24	1.52		1097	1.36	1.28	1.44
	Unspecified kidney failure	139	1.43	1.20	1.69		71	1.35	1.05	1.70		210	1.40	1.22	1.60
	All kidney failure	1124	1.28	1.21	1.36		637	1.32	1.22	1.43		1761	1.29	1.23	1.35
Paternal history															
Acute kidney failure	Acute kidney failure	62	1.20	0.92	1.54		26	1.03	0.67	1.51		88	1.14	0.92	1.41
	Chronic kidney failure	96	1.03	0.83	1.26		53	1.01	0.76	1.32		149	1.02	0.86	1.20
	Unspecified kidney failure	27	1.49	0.98	2.18		15	1.31	0.73	2.17		42	1.42	1.03	1.93
	All kidney failure	185	1.13	0.98	1.31		94	1.06	0.85	1.29		279	1.11	0.98	1.24
Chronic kidney failure	Acute kidney failure	82	1.32	1.05	1.64		43	1.21	0.87	1.63		125	1.28	1.07	1.53
	Chronic kidney failure	212	1.73	1.50	1.98		105	1.45	1.19	1.76		317	1.62	1.45	1.81
	Unspecified kidney failure	41	1.91	1.37	2.59		18	1.40	0.83	2.22		59	1.72	1.31	2.22
	All kidney failure	335	1.63	1.46	1.81		166	1.37	1.17	1.60		501	1.53	1.40	1.67
Unspecified kidney failure	Acute kidney failure	30	1.00	0.67	1.43		19	1.13	0.68	1.77		49	1.05	0.77	1.38
	Chronic kidney failure	78	1.26	0.99	1.57		36	0.96	0.67	1.33		114	1.14	0.94	1.38
	Unspecified kidney failure	9	0.74	0.33	1.40		11	1.87	0.93	3.36		20	1.10	0.67	1.71
	All kidney failure	117	1.12	0.93	1.34		66	1.09	0.85	1.39		183	1.11	0.96	1.29
All kidney failure	Acute kidney failure	174	1.21	1.04	1.41		88	1.13	0.91	1.40		262	1.18	1.04	1.34
	Chronic kidney failure	386	1.39	1.25	1.53		194	1.19	1.03	1.38		580	1.32	1.21	1.43
	Unspecified kidney failure	77	1.49	1.17	1.86		44	1.46	1.06	1.96		121	1.48	1.23	1.77
	All kidney failure	637	1.35	1.24	1.45		326	1.21	1.08	1.35		963	1.29	1.21	1.38
Maternal history															
Acute kidney failure	Acute kidney failure	42	0.92	0.66	1.25		33	1.19	0.82	1.67		75	1.02	0.80	1.28
	Chronic kidney failure	94	0.97	0.79	1.19		59	1.29	0.98	1.66		153	1.07	0.91	1.26
	Unspecified kidney failure	23	1.26	0.80	1.89		9	1.05	0.48	2.00		32	1.19	0.81	1.68
	All kidney failure	159	0.99	0.84	1.16		101	1.23	1.00	1.49		260	1.07	0.95	1.21

Chronic kidney failure	Acute kidney failure	38	0.70	0.50	0.97		42	1.64	1.18	2.22		80	1.01	0.80	1.25
	Chronic kidney failure	178	1.69	1.45	1.96		108	1.88	1.54	2.27		286	1.76	1.56	1.97
	Unspecified kidney failure	29	1.55	1.04	2.23		13	1.24	0.66	2.12		42	1.44	1.04	1.95
	All kidney failure	245	1.38	1.21	1.56		163	1.74	1.49	2.03		408	1.50	1.36	1.66
Unspecified kidney failure	Acute kidney failure	30	1.18	0.80	1.69		13	0.89	0.47	1.52		43	1.08	0.78	1.45
	Chronic kidney failure	66	1.23	0.95	1.56		42	1.56	1.12	2.11		108	1.34	1.10	1.62
	Unspecified kidney failure	13	1.26	0.67	2.16		7	1.39	0.55	2.89		20	1.31	0.80	2.02
	All kidney failure	109	1.22	1.00	1.47		62	1.33	1.02	1.71		171	1.26	1.08	1.46
All kidney failure	Acute kidney failure	110	0.88	0.72	1.06		88	1.29	1.04	1.59		198	1.03	0.89	1.18
	Chronic kidney failure	338	1.32	1.19	1.47		209	1.60	1.39	1.84		547	1.42	1.30	1.54
	Unspecified kidney failure	65	1.38	1.06	1.75		29	1.20	0.80	1.73		94	1.32	1.06	1.61
	All kidney failure	513	1.20	1.10	1.31		326	1.47	1.31	1.63		839	1.29	1.21	1.38
Sibling history															
Acute kidney failure	Acute kidney failure	52	1.15	0.86	1.50		27	0.98	0.64	1.43		79	1.08	0.86	1.35
	Chronic kidney failure	97	1.19	0.97	1.45		42	1.09	0.79	1.47		139	1.16	0.97	1.37
	Unspecified kidney failure	16	1.08	0.62	1.77		12	1.44	0.74	2.52		28	1.21	0.80	1.75
	All kidney failure	165	1.17	0.99	1.36		81	1.09	0.86	1.35		246	1.14	1.00	1.29
Chronic kidney failure	Acute kidney failure	88	1.25	1.00	1.54		49	1.09	0.81	1.44		137	1.19	1.00	1.40
	Chronic kidney failure	366	2.52	2.27	2.80		213	2.52	2.19	2.88		579	2.52	2.32	2.73
	Unspecified kidney failure	42	1.42	1.02	1.92		36	2.14	1.50	2.97		78	1.68	1.33	2.10
	All kidney failure	496	2.02	1.85	2.21		298	2.04	1.81	2.28		794	2.03	1.89	2.18
Unspecified kidney failure	Acute kidney failure	17	1.10	0.64	1.77		13	1.32	0.70	2.26		30	1.19	0.80	1.70
	Chronic kidney failure	48	1.58	1.16	2.09		32	1.86	1.27	2.63		80	1.68	1.33	2.09
	Unspecified kidney failure	12	1.65	0.85	2.89		6	1.08	0.39	2.37		18	1.40	0.83	2.22
	All kidney failure	77	1.45	1.14	1.81		51	1.56	1.16	2.06		128	1.49	1.25	1.78
All kidney failure	Acute kidney failure	157	1.20	1.02	1.40		89	1.08	0.87	1.33		246	1.15	1.01	1.31
	Chronic kidney failure	511	1.99	1.82	2.17		287	2.04	1.81	2.30		798	2.01	1.87	2.15
	Unspecified kidney failure	70	1.36	1.06	1.72		54	1.76	1.32	2.30		124	1.51	1.25	1.80
	All kidney failure	738	1.68	1.56	1.80		430	1.70	1.54	1.87		1168	1.69	1.59	1.78

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00.
O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Table 19 shows age stratified concordant and discordant familial risks (parent/siblings) of kidney failure. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Results were similarl to the familial age stratified concordant risks in Table 16. Thus, age stratified concordant and discordant risks were generally highest for chronic kidney failure, followed by unspecified kidney failure, and weakest for acute kidney failure independent of the type of affected relative (sibling/parent, parents, mother, father or sibling). However, for acute kidney failure, the familial concordant risks were highly increased in the two youngest age groups (Table 19).

Table 19.
Familial risk (sibling/parent history) of concordant and discordant kidney failure in males and females by age at diagnosis

		Males				Females				All			
Kidney failure in probands	Age at diagnosis (years) of subtype of kidney failure	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Acute kidney failure	Acute kidney failure												
	<10	4	16.78	4.36	43.39	2	10.88	1.03	40.02	6	14.21	5.11	31.14
	10-19	0				0				0			
	20-29	6	2.00	0.72	4.37	5	3.70	1.17	8.70	11	2.52	1.25	4.53
	30-39	11	1.43	0.71	2.57	2	0.61	0.06	2.24	13	1.18	0.63	2.03
	40-49	22	1.23	0.77	1.87	14	1.57	0.86	2.64	36	1.34	0.94	1.86
	50-59	52	1.35	1.01	1.78	21	0.84	0.52	1.28	73	1.15	0.90	1.45
	>=60	58	0.80	0.61	1.03	40	0.99	0.71	1.35	98	0.87	0.70	1.06
	All	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure												
	<10	0				1	5.59	0.00	32.04	1	2.23	0.00	12.77
	10-19	1	0.99	0.00	5.67	2	3.63	0.34	13.36	3	1.92	0.36	5.69
	20-29	3	0.59	0.11	1.75	2	0.54	0.05	2.00	5	0.57	0.18	1.34
	30-39	21	1.10	0.68	1.68	15	1.25	0.70	2.07	36	1.16	0.81	1.60
	40-49	43	0.98	0.71	1.32	26	1.09	0.71	1.60	69	1.02	0.79	1.29
	50-59	95	1.19	0.96	1.45	53	1.40	1.05	1.83	148	1.26	1.06	1.48
	>=60	119	1.04	0.86	1.25	54	0.99	0.74	1.29	173	1.02	0.88	1.19
	All	282	1.07	0.95	1.20	153	1.15	0.98	1.35	435	1.10	1.00	1.21
	Unspecified kidney failure												
	<10	0				0				0			
	10-19	0				0				0			
	20-29	2	3.07	0.29	11.31	0				2	1.74	0.16	6.41
	30-39	2	0.76	0.07	2.80	0				2	0.44	0.04	1.61
	40-49	7	0.90	0.36	1.86	7	1.15	0.46	2.39	14	1.01	0.55	1.70
	50-59	19	1.35	0.81	2.11	9	1.16	0.53	2.22	28	1.28	0.85	1.86
	>=60	34	1.41	0.97	1.97	20	1.80	1.10	2.78	54	1.53	1.15	2.00
	All	64	1.29	1.00	1.65	36	1.31	0.92	1.81	100	1.30	1.06	1.58

	All kidney failure												
	<10	4	7.27	1.89	18.79		3	7.25	1.37	21.47	7	7.26	2.88	15.04
	10-19	1	0.51	0.00	2.90		2	1.52	0.14	5.60	3	0.91	0.17	2.70
	20-29	11	1.26	0.62	2.26		7	1.26	0.50	2.62	18	1.26	0.75	2.00
	30-39	34	1.15	0.80	1.61		17	0.99	0.57	1.58	51	1.09	0.81	1.44
	40-49	72	1.04	0.81	1.31		47	1.21	0.89	1.61	119	1.10	0.91	1.32
	50-59	166	1.25	1.07	1.46		83	1.17	0.94	1.46	249	1.23	1.08	1.39
	>=60	211	1.00	0.87	1.14		114	1.07	0.89	1.29	325	1.02	0.92	1.14
	All	499	1.10	1.01	1.20		273	1.14	1.01	1.28	772	1.11	1.04	1.19
Chronic kidney failure	Acute kidney failure													
	<10	0					3	6.15	1.16	18.22	3	3.06	0.58	9.07
	10-19	0					3	1.61	0.30	4.77	3	0.93	0.18	2.76
	20-29	8	1.36	0.58	2.69		3	0.99	0.19	2.93	11	1.23	0.61	2.22
	30-39	19	1.18	0.71	1.85		7	1.18	0.47	2.45	26	1.18	0.77	1.74
	40-49	34	1.44	0.99	2.01		17	1.18	0.68	1.89	51	1.34	1.00	1.76
	50-59	59	1.23	0.94	1.59		29	1.03	0.69	1.48	88	1.16	0.93	1.42
	>=60	81	1.02	0.81	1.26		67	1.38	1.07	1.75	148	1.15	0.97	1.35
	All	201	1.15	0.99	1.32		129	1.26	1.05	1.50	330	1.19	1.06	1.32
	Chronic kidney failure													
	<10	2	3.92	0.37	14.41		0				2	2.09	0.20	7.70
	10-19	16	6.94	3.96	11.30		11	5.60	2.78	10.06	27	6.33	4.16	9.22
	20-29	41	4.87	3.49	6.61		33	4.35	2.99	6.12	74	4.62	3.63	5.81
	30-39	91	2.36	1.90	2.90		43	1.76	1.27	2.37	134	2.13	1.78	2.52
	40-49	135	2.08	1.75	2.47		75	2.11	1.66	2.65	210	2.09	1.82	2.40
	50-59	187	1.86	1.60	2.14		92	1.74	1.40	2.14	279	1.82	1.61	2.04
	>=60	245	1.81	1.59	2.05		141	1.81	1.52	2.14	386	1.81	1.63	2.00
	All	717	2.04	1.90	2.20		395	1.97	1.78	2.17	1112	2.02	1.90	2.14
	Unspecified kidney failure													
	<10	0					0				0			
	10-19	4	13.55	3.52	35.03		2	9.12	0.86	33.52	6	11.66	4.20	25.54
	20-29	4	2.44	0.63	6.30		5	4.40	1.39	10.35	9	3.24	1.47	6.18
	30-39	15	3.12	1.74	5.17		9	2.56	1.16	4.88	24	2.88	1.85	4.30
	40-49	18	1.76	1.04	2.79		14	2.48	1.35	4.17	32	2.01	1.38	2.85
	50-59	27	1.38	0.91	2.01		15	1.39	0.77	2.30	42	1.38	1.00	1.87
	>=60	36	1.20	0.84	1.67		20	1.29	0.79	2.00	56	1.23	0.93	1.60
	All	104	1.56	1.28	1.89		65	1.76	1.36	2.24	169	1.63	1.40	1.90

	All kidney failure												
	<10	2	1.82	0.17	6.70		3	2.73	0.51	8.08	5	2.28	0.72	5.36
	10-19	20	5.05	3.08	7.81		16	3.96	2.26	6.44	36	4.50	3.15	6.23
	20-29	53	3.32	2.49	4.35		41	3.49	2.50	4.74	94	3.39	2.74	4.15
	30-39	125	2.11	1.75	2.51		59	1.74	1.32	2.25	184	1.97	1.70	2.28
	40-49	187	1.89	1.63	2.19		106	1.91	1.56	2.31	293	1.90	1.69	2.13
	50-59	273	1.62	1.43	1.83		136	1.48	1.24	1.75	409	1.57	1.42	1.73
	>=60	362	1.48	1.33	1.64		228	1.61	1.41	1.83	590	1.52	1.40	1.65
	All	1022	1.72	1.62	1.83		589	1.73	1.59	1.88	1611	1.73	1.64	1.81
Unspecified kidney failure	Acute kidney failure													
	<10	0					0				0			
	10-19	0					2	7.22	0.68	26.56	2	4.33	0.41	15.91
	20-29	0					2	3.67	0.35	13.49	2	1.17	0.11	4.31
	30-39	2	0.72	0.07	2.65		0	0.00	0.61	2.47	2	0.46	0.04	1.69
	40-49	8	1.02	0.44	2.03		3	0.83	0.16	2.45	11	0.96	0.48	1.73
	50-59	22	1.15	0.72	1.74		9	0.74	0.33	1.41	31	0.99	0.67	1.40
	>=60	40	1.12	0.80	1.52		26	1.18	0.77	1.73	66	1.14	0.88	1.45
	All	72	1.07	0.84	1.35		42	1.04	0.75	1.41	114	1.06	0.88	1.28
	Chronic kidney failure													
	<10	0					0				0			
	10-19	2	4.55	0.43	16.72		4	13.32	3.46	34.43	6	8.10	2.92	17.76
	20-29	7	3.16	1.25	6.55		5	2.90	0.91	6.81	12	3.04	1.57	5.34
	30-39	13	1.31	0.69	2.24		10	1.84	0.88	3.40	23	1.49	0.95	2.25
	40-49	21	1.06	0.65	1.62		18	1.47	0.87	2.32	39	1.21	0.86	1.66
	50-59	46	1.25	0.92	1.67		28	1.31	0.87	1.89	74	1.27	1.00	1.60
	>=60	87	1.33	1.07	1.64		36	1.01	0.71	1.40	123	1.22	1.01	1.45
	All	176	1.31	1.12	1.52		101	1.31	1.07	1.60	277	1.31	1.16	1.47
	Unspecified kidney failure													
	<10	0					0				0			
	10-19	0					0				0			
	20-29	1	2.39	0.00	13.67		1	4.41	0.00	25.26	2	3.10	0.29	11.38
	30-39	6	2.80	1.01	6.12		1	1.04	0.00	5.95	7	2.25	0.89	4.66
	40-49	2	0.58	0.05	2.12		4	1.62	0.42	4.18	6	1.01	0.36	2.21
	50-59	8	1.04	0.45	2.07		4	1.18	0.31	3.05	12	1.09	0.56	1.90
	>=60	16	1.13	0.64	1.83		11	1.35	0.67	2.43	27	1.21	0.80	1.76
	All	33	1.18	0.81	1.65		21	1.38	0.85	2.11	54	1.25	0.94	1.63

	All kidney failure												
	<10	0				0				0			
	10-19	2	2.59	0.24	9.53	6	9.67	3.48	21.19	8	5.75	2.45	11.38
	20-29	8	2.11	0.90	4.17	8	3.20	1.37	6.34	16	2.54	1.45	4.14
	30-39	21	1.41	0.87	2.16	11	1.38	0.68	2.47	32	1.40	0.96	1.98
	40-49	31	1.00	0.68	1.42	25	1.36	0.88	2.01	56	1.13	0.85	1.47
	50-59	76	1.20	0.94	1.50	41	1.11	0.79	1.50	117	1.16	0.96	1.40
	>=60	143	1.24	1.05	1.46	73	1.11	0.87	1.39	216	1.19	1.04	1.36
	All	281	1.22	1.09	1.38	164	1.24	1.06	1.44	445	1.23	1.12	1.35
All kidney failure	Acute kidney failure												
	<10	4	5.00	1.30	12.93	5	6.76	2.13	15.90	9	5.84	2.65	11.14
	10-19	0				5	1.78	0.56	4.20	5	0.97	0.31	2.28
	20-29	14	1.39	0.76	2.34	10	2.03	0.97	3.74	24	1.60	1.03	2.39
	30-39	32	1.21	0.83	1.71	9	0.83	0.38	1.59	41	1.10	0.79	1.49
	40-49	64	1.30	1.00	1.66	34	1.26	0.87	1.76	98	1.28	1.04	1.57
	50-59	133	1.26	1.05	1.49	59	0.90	0.69	1.17	192	1.12	0.97	1.29
	>=60	179	0.95	0.82	1.10	133	1.20	1.00	1.42	312	1.04	0.93	1.16
	All	426	1.11	1.01	1.22	255	1.15	1.01	1.30	681	1.12	1.04	1.21
	Chronic kidney failure												
	<10	2	2.30	0.22	8.47	1	1.38	0.00	7.90	3	1.88	0.35	5.57
	10-19	19	5.06	3.04	7.91	17	6.04	3.51	9.69	36	5.48	3.84	7.59
	20-29	51	3.24	2.41	4.27	40	3.08	2.20	4.19	91	3.17	2.55	3.89
	30-39	125	1.85	1.54	2.20	68	1.62	1.26	2.06	193	1.76	1.52	2.03
	40-49	199	1.55	1.34	1.78	119	1.66	1.38	1.99	318	1.59	1.42	1.77
	50-59	328	1.51	1.35	1.68	173	1.54	1.32	1.79	501	1.52	1.39	1.66
	>=60	451	1.43	1.30	1.57	231	1.37	1.20	1.56	682	1.41	1.31	1.52
	All	1175	1.57	1.48	1.66	649	1.58	1.46	1.71	1824	1.57	1.50	1.65
	Unspecified kidney failure												
	<10	0				0				0			
	10-19	4	6.60	1.72	17.07	2	5.57	0.53	20.49	6	6.22	2.24	13.63
	20-29	7	2.58	1.02	5.35	6	3.22	1.16	7.07	13	2.84	1.51	4.88
	30-39	23	2.40	1.52	3.61	10	1.56	0.74	2.88	33	2.06	1.42	2.90
	40-49	27	1.26	0.83	1.83	25	1.76	1.14	2.60	52	1.46	1.09	1.91
	50-59	54	1.31	0.98	1.71	28	1.28	0.85	1.85	82	1.30	1.03	1.61
	>=60	86	1.26	1.01	1.56	51	1.47	1.09	1.93	137	1.33	1.12	1.57
	All	201	1.39	1.21	1.60	122	1.53	1.27	1.83	323	1.44	1.29	1.61

	All kidney failure												
	<10	6	3.28	1.18	7.19		6	3.52	1.27	7.71	12	3.40	1.75	5.95
	10-19	23	3.43	2.17	5.15		24	4.02	2.57	5.98	47	3.70	2.72	4.93
	20-29	72	2.53	1.98	3.18		56	2.83	2.14	3.68	128	2.65	2.21	3.15
	30-39	180	1.74	1.49	2.01		87	1.47	1.18	1.82	267	1.64	1.45	1.85
	40-49	290	1.45	1.29	1.63		178	1.58	1.36	1.83	468	1.50	1.37	1.64
	50-59	515	1.41	1.29	1.54		260	1.30	1.15	1.47	775	1.37	1.28	1.47
	>=60	716	1.25	1.16	1.35		415	1.32	1.20	1.46	1131	1.28	1.20	1.35
	All	1802	1.41	1.35	1.48		1026	1.44	1.35	1.53	2828	1.42	1.37	1.48

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00. O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Sensitivity analysis

Concordant and discordant familial risks (parent/siblings) were analysed after exclusion of patients with kidney cancer in parents/offspring. The results did not change to any major degree (Table 20).

Table 21 shows concordant and discordant familial risks (parent/siblings) for the follow-up period 2001-2010. Compared to follow-up period 1987-2010, the familial risks did not change to any major degree. Thus, the inclusion of outpatients with kidney failure diagnosis from 2001-2010 did not change the results to any major degree (Table 21).

Table 20.
Familial risk (sibling/offspring) of concordant and discordant kidney failure in males and females, after excluding kidney cancer in parents/ offspring.

	Males				Females				All			
Subtype of kidney failure in offspring/siblings	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Probands with Acute kidney failure												
Acute kidney failure	148	1.08	0.91	1.27	82	1.05	0.83	1.30	230	1.07	0.93	1.21
Chronic kidney failure	275	1.07	0.95	1.21	151	1.17	0.99	1.37	426	**1.10**	**1.00**	**1.21**
Unspecified kidney failure	60	1.26	0.96	1.62	35	1.32	0.92	1.84	95	**1.28**	**1.04**	**1.57**
All kidney failure	483	**1.09**	**1.00**	**1.20**	268	**1.14**	**1.01**	**1.29**	751	**1.11**	**1.03**	**1.19**
Probands with Chronic kidney failure												
Acute kidney failure	196	1.15	0.99	1.32	125	**1.25**	**1.04**	**1.49**	321	**1.18**	**1.06**	**1.32**
Chronic kidney failure	693	**2.05**	**1.90**	**2.20**	387	**1.98**	**1.79**	**2.19**	1080	**2.02**	**1.90**	**2.15**
Unspecified kidney failure	102	**1.59**	**1.30**	**1.93**	64	**1.76**	**1.36**	**2.25**	166	**1.65**	**1.41**	**1.93**
All kidney failure	991	**1.73**	**1.62**	**1.84**	576	**1.74**	**1.60**	**1.88**	1567	**1.73**	**1.65**	**1.82**
Probands with unspecified kidney failure												
Acute kidney failure	72	1.11	0.87	1.40	41	1.04	0.75	1.41	113	1.08	0.89	1.30
Chronic kidney failure	166	**1.28**	**1.10**	**1.49**	96	**1.28**	**1.04**	**1.56**	262	**1.28**	**1.13**	**1.45**
Unspecified kidney failure	33	1.23	0.85	1.73	21	1.41	0.87	2.16	54	1.30	0.97	1.69
All kidney failure	271	**1.23**	**1.08**	**1.38**	158	**1.22**	**1.04**	**1.43**	429	**1.22**	**1.11**	**1.35**
Probands with all types of kidney failure												
Acute kidney failure	416	**1.11**	**1.01**	**1.23**	248	**1.14**	**1.00**	**1.29**	664	**1.12**	**1.04**	**1.21**
Chronic kidney failure	1134	**1.57**	**1.48**	**1.66**	634	**1.58**	**1.46**	**1.71**	1768	**1.57**	**1.50**	**1.65**
Unspecified kidney failure	195	**1.41**	**1.22**	**1.62**	120	**1.55**	**1.28**	**1.85**	315	**1.46**	**1.30**	**1.63**
All kidney failure	1745	**1.41**	**1.35**	**1.48**	1002	**1.44**	**1.35**	**1.53**	2747	**1.42**	**1.37**	**1.48**

Table 21 shows concordant and discordant familial risks (parent/siblings) for the follow up period 2001-2010. The familial risks were similar compared to using a follow-up period from 1987-2010. Thus, inclusion of outpatients with kidney failure diagnosis from 2001 until 2010 did not change the results to any major degree.

Table 21.
Familial risk of concordant and discordant kidney failure in males and females, follow-up 2001-2010

		Males				Females				All			
Probands with any type of kidney failure	Subtype of kidney failure in offspring/siblings	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Acute kidney failure	Acute kidney failure	111	1.10	0.90	1.32	66	1.10	0.85	1.40	177	1.10	0.94	1.27
	Chronic kidney failure	214	1.08	0.94	1.23	112	1.05	0.87	1.27	326	1.07	0.95	1.19
	Unspecified kidney failure	54	1.58	1.19	2.06	27	1.49	0.98	2.16	81	1.55	1.23	1.92
	All kidney failure	379	1.13	1.02	1.25	205	1.11	0.96	1.28	584	1.13	1.04	1.22
Chronic kidney failure	Acute kidney failure	158	1.15	0.98	1.34	104	1.39	1.14	1.69	262	1.24	1.09	1.39
	Chronic kidney failure	525	1.93	1.76	2.10	301	1.90	1.69	2.13	826	1.92	1.79	2.05
	Unspecified kidney failure	68	1.42	1.10	1.80	38	1.52	1.07	2.08	106	1.45	1.19	1.76
	All kidney failure	751	1.64	1.52	1.76	443	1.72	1.56	1.89	1194	1.67	1.57	1.77
Unspecified kidney failure	Acute kidney failure	55	1.03	0.78	1.35	34	1.07	0.74	1.49	89	1.05	0.84	1.29
	Chronic kidney failure	135	1.26	1.05	1.49	71	1.15	0.90	1.45	206	1.22	1.06	1.40
	Unspecified kidney failure	23	1.17	0.74	1.76	13	1.19	0.63	2.04	36	1.18	0.82	1.63
	All kidney failure	213	1.18	1.03	1.35	118	1.13	0.93	1.35	331	1.16	1.04	1.29
All kidney failure	Acute kidney failure	324	1.11	0.99	1.24	204	1.23	1.06	1.41	528	1.15	1.06	1.25
	Chronic kidney failure	874	1.51	1.41	1.61	484	1.48	1.35	1.62	1358	1.50	1.42	1.58
	Unspecified kidney failure	145	1.43	1.20	1.68	78	1.44	1.14	1.80	223	1.43	1.25	1.63
	All kidney failure	1343	1.38	1.31	1.46	766	1.40	1.30	1.50	2109	1.39	1.33	1.45

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00. O = observed number of cases with family history of kidney failure; SIR = standardised incidence ratio; CI = confidence interval

Familial risk of ESRD treated with chronic dialysis or kidney transplantation

In addition to published paper II, calculations using the severe ESRD phenotype used in paper IV have been performed. ESRD was defined by chronic dialysis or kidney transplantation (Table 3). The familial SIR (concordant only for parent offspring and siblings) for kidney failure with new definition of end-stage renal disease (ESRD) during follow up period 1987—2012. The familial SIR was even higher than determined in paper II when using this severe phenotype of ESRD. The familial SIR for all individuals with a sibling history of kidney failure was 5.59 (95% CI 5,20- 6.01) (Table 22).

Table 22.
Calculate the familial SIR for end-stage renal disease (ESRD) treated with chronic dialysis or kidney transplantation.

Probands	Men				Women				All			
	Cases	SIR	95% CI		Cases	SIR	95% CI		Cases	SIR	95% CI	
Family history	705	4.38	4.06	4.72	480	5.22	4.76	5.71	1185	4.68	4.42	4.96
Parental history	350	4.27	3.84	4.75	204	4.15	3.60	4.76	554	4.23	3.88	4.59
Sibling history	420	4.95	4.49	5.45	318	6.74	6.02	7.52	738	5.59	5.20	6.01

Population characteristics study III

In study III we analysed the familial risks of glomerulonephritis defined as acute, chronic and unspecified glomerulonephritis (not acute or chronic) in the full-siblings/offspring aged 0-78 years. A total of 8187887 individuals were assessed in the registers for a clinical diagnosis of glomerulonephritis between 1964-2010 in Sweden. A total of 23 015 individuals were diagnosed with glomerulonephritis; 14009 (61%) males and 9006 (39%) females. Of all diagnosed cases, 7011 (30.5%) were acute glomerulonephritis, 10242 (44.5%) were chronic glomerulonephritis and 5762 (25%) were unspecified glomerulonephritis. Mostly, individuals diagnosed with glomerulonephritis were at a young age. The characteristics of patients are presented in Table 23.

Table 23.
Characteristics of Swedish patients with glomerulonephritis diagnosed between 1964 and 2010 and born between 1932 until 2010.

	Males			Females			All	
	No	%		No	%		No	%
Subtype of glomerulonephritis								
Acute	4357	31.1		2654	29.5		7011	30.5
Chronic	6446	46.0		3796	42.1		10242	44.5
Unspecified	3206	22.9		2556	28.4		5762	25.0
Age at diagnosis (yrs)								
<10	2297	16.4		1526	16.9		3823	16.6
10-19	2595	18.5		1629	18.1		4224	18.4
20-29	2459	17.6		1572	17.5		4031	17.5
30-39	2223	15.9		1455	16.2		3678	16.0
40-49	1740	12.4		1106	12.3		2846	12.4
50-59	1512	10.8		983	10.9		2495	10.8
60-69	986	7.0		601	6.7		1587	6.9
≥ 70	197	1.4		134	1.5		331	1.4
Periods (years)								
1964-73	1231	8.8		758	8.4		1989	8.6
1974-83	3398	24.3		1887	21.0		5285	23.0
1984-93	2626	18.7		1612	17.9		4238	18.4
1994-03	3459	24.7		2215	24.6		5674	24.7
2004-10	3295	23.5		2534	28.1		5829	25.3
Socioeconomic status								
Farmers	251	1.8		114	1.3		365	1.6
Self-employed workers	703	5.0		306	3.4		1009	4.4
Professionals	1507	10.8		583	6.5		2090	9.1
White-collar workers	4231	30.2		3529	39.2		7760	33.7
Blue-collar workers	7010	50.0		4233	47.0		11243	48.9
Others	307	2.2		241	2.7		548	2.4
Region of residence								
Large cities	5671	40.5		3819	42.4		9490	41.2
Southern Sweden	5972	42.6		3788	42.1		9760	42.4
Northern Sweden	2366	16.9		1399	15.5		3765	16.4
All	14009	100.0		9006	100.0		23015	100.0

Familial risks of glomerulonephritis

Increased familial risks for glomerulonephritis were observed for paternal, maternal, and full sibling history of glomerulonephritis (Table 23). Chronic glomerulonephritis presented the highest risks in all lines; SIR for chronic glomerulonephritis in siblings was 3.73 (95% CI 3.26-4.26). The familial SIR in siblings for acute glomerulonephritis was 2.93 (95% CI 2.38-3.56) and for unspecified glomerulonephritis it was 3.37 (95% CI 2.75-4.10). Familial risks of glomerulonephritis were increased in both males and females, Table 24. The sibling risks were generally higher than parent-offspring risks.

Table 24.
Familial risks of glomerulonephritis (acute, chronic and unspecified) according to relatedness.

		Males				Females				All			
Relatives with any type of glomerulonephritis	Subtype of glomerulonephritis in cases	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Parents history	Acute	60	1.68	1.28	2.16	34	1.57	1.09	2.20	94	1.64	1.32	2.01
	Chronic	156	2.97	2.52	3.47	109	3.53	2.90	4.26	265	3.18	2.81	3.58
	Unspecified	67	2.58	2.00	3.28	51	2.49	1.86	3.28	118	2.54	2.11	3.05
	All	283	2.48	2.20	2.78	194	2.66	2.30	3.06	477	2.55	2.33	2.79
Paternal history	Acute	38	1.74	1.23	2.39	19	1.44	0.86	2.25	57	1.63	1.23	2.11
	Chronic	93	2.93	2.36	3.59	62	3.28	2.52	4.21	155	3.06	2.60	3.58
	Unspecified	39	2.47	1.76	3.38	27	2.17	1.43	3.17	66	2.34	1.81	2.98
	All	170	2.45	2.10	2.85	108	2.43	1.99	2.93	278	2.44	2.16	2.75
Maternal history	Acute	24	1.70	1.09	2.53	16	1.88	1.07	3.06	40	1.77	1.26	2.41
	Chronic	63	2.94	2.26	3.77	47	3.79	2.78	5.04	110	3.25	2.67	3.92
	Unspecified	29	2.79	1.87	4.01	24	2.92	1.87	4.35	53	2.85	2.13	3.72
	All	116	2.53	2.09	3.03	87	2.99	2.39	3.68	203	2.70	2.34	3.10
Sibling history*	Acute	68	3.11	2.42	3.95	32	2.60	1.78	3.67	100	2.93	2.38	3.56
	Chronic	143	3.72	3.14	4.39	81	3.75	2.98	4.66	224	3.73	3.26	4.26
	Unspecified	68	3.97	3.08	5.04	33	2.57	1.77	3.61	101	3.37	2.75	4.10
	All	279	3.61	3.20	4.06	146	3.12	2.64	3.67	425	3.42	3.11	3.77
Spouse	Any types of glomerulonephritis	105	1.54	1.26	1.86	105	1.52	1.24	1.84	210	1.53	1.33	1.75

Bold type: 95% CI does not include 1.00.
O = observed number of cases; SIR = standardised incidence ratio; CI = confidence interval
Familial risks were adjusted for age, sex, time period, region of residence and socioeconomic status. *Only individuals with at least one full-sibling were included in the analysis.

Familial risks of glomerulonephritis in different ages

Familial risks were high in all age groups (Table 25). The parent-offspring risk was highest among individuals aged 30-39 years SIR= 3.38 (95% CI 2.76-4.10). The sibling risk was highest for individuals aged 20-29 years SIR= 4.74 (95% CI 3.85-5.78).

Table 25.
Age- and sex-stratified familial risks of glomerulonephritis.

	Males				Females				All			
Age at diagnosis (years)	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Parental history												
<10	32	**1.68**	**1.15**	**2.38**	25	**2.04**	**1.32**	**3.02**	57	**1.83**	**1.38**	**2.37**
10-19	54	**2.44**	**1.83**	**3.18**	37	**2.71**	**1.91**	**3.74**	91	**2.54**	**2.05**	**3.12**
20-29	54	**2.60**	**1.96**	**3.40**	44	**3.37**	**2.45**	**4.53**	98	**2.90**	**2.36**	**3.54**
30-39	63	**3.42**	**2.63**	**4.37**	40	**3.31**	**2.37**	**4.52**	103	**3.38**	**2.76**	**4.10**
40-49	42	**2.96**	**2.13**	**4.01**	25	**2.71**	**1.75**	**4.01**	67	**2.86**	**2.22**	**3.64**
50-59	28	**2.38**	**1.58**	**3.44**	14	1.79	0.98	3.01	42	**2.14**	**1.54**	**2.90**
>=60	10	1.26	0.60	2.33	9	1.85	0.84	3.52	19	1.48	0.89	2.32
All	283	**2.48**	**2.20**	**2.78**	194	**2.66**	**2.30**	**3.06**	477	**2.55**	**2.33**	**2.79**
Full-sibling history*												
<10	28	**3.38**	**2.25**	**4.90**	9	1.79	0.81	3.42	37	**2.78**	**1.96**	**3.84**
10-19	65	**5.15**	**3.98**	**6.57**	26	**3.86**	**2.52**	**5.66**	91	**4.70**	**3.79**	**5.78**
20-29	61	**4.66**	**3.56**	**5.99**	38	**4.88**	**3.45**	**6.71**	99	**4.74**	**3.85**	**5.78**
30-39	50	**3.74**	**2.77**	**4.93**	20	**2.33**	**1.42**	**3.60**	70	**3.19**	**2.48**	**4.03**
40-49	26	**2.23**	**1.46**	**3.27**	26	**3.67**	**2.40**	**5.39**	52	**2.77**	**2.07**	**3.64**
50-59	25	**2.44**	**1.58**	**3.60**	19	**2.88**	**1.73**	**4.51**	44	**2.61**	**1.90**	**3.51**
>=60	24	**3.04**	**1.95**	**4.54**	8	1.62	0.69	3.20	32	**2.49**	**1.70**	**3.52**
All	279	**3.61**	**3.20**	**4.06**	146	**3.12**	**2.64**	**3.67**	425	**3.42**	**3.11**	**3.77**

Bold type: 95% CI does not include 1.00.
O = observed number of cases; SIR = standardised incidence ratio; CI = confidence interval
Familial risks were adjusted for age, sex, time period, region of residence and socioeconomic status. *Only individuals with at least one sibling were included in the analysis.

Sex differences for familial risks of glomerulonephritis

Sex differences were calculated by estimating family risk ratios and incidence rate ratios for glomerulonephritis in males and females. The SIR ratio (male/female) was 1.15 (95% CI 0.95-1.35), p= 0.1553. The incidence rate ratio (male/female) was 1.52 (95% CI 1.47-1.56) p<0.001. The calculations were based on an incidence rate of 10.9 per 100,000 person years for males and 7.2 per 100,000 person years for females. Age. and sex specific incidence rates of glomerulonephritis are presented in Figure 4 and Figure 5.

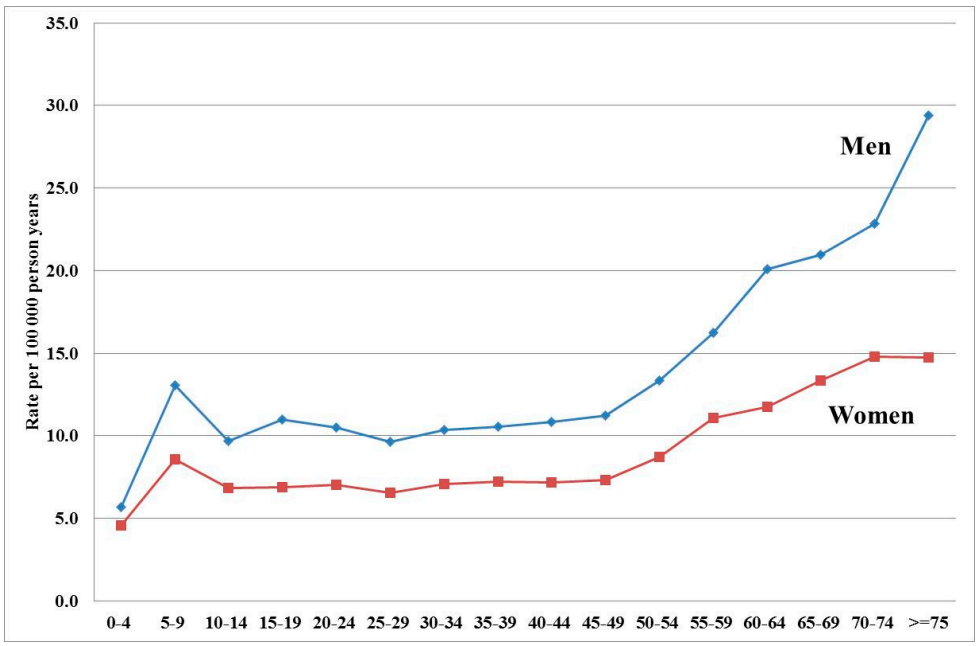
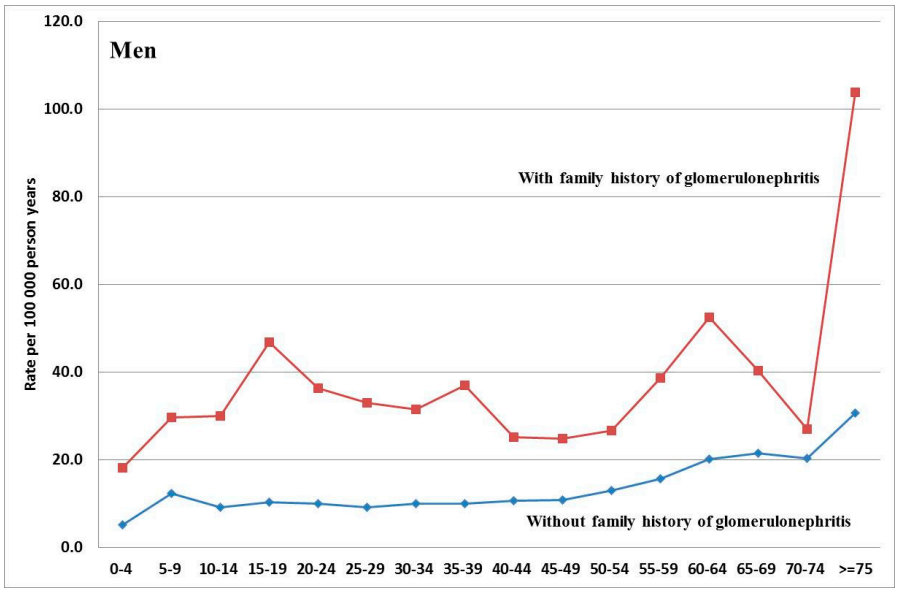


Figure 4.
Age- and sex-specific incidence of glomerulonephritis in the Swedish population aged 0-78 years between 1964 and 2010.



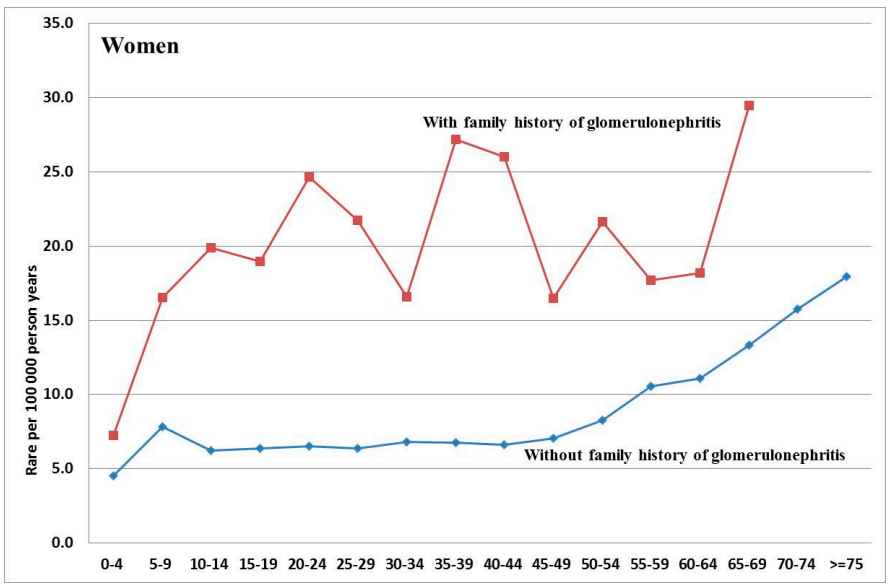


Figure 5.
Age- and sex-specific incidence of glomerulonephritis in the Swedish population aged 0-78 years between 1964 and 2010 by presence or absence of family history (parent/full-sibling) of glomerulonephritis.

Discordant familial risks of glomerulonephritis

Familial risks of concordant (same disease in proband and relative) and discordant (different disease in proband and relative) for glomerulonephritis are presented in Table 26. Higher familial risks for individuals with affected family members (family history) of all types of glomerulonephritis were observed. Among individuals with a family history (sibling/parent) of acute glomerulonephritis the concordant familial SIR was 3.57 (95% CI 2.77-4.53). For chronic glomerulonephritis the SIR was 3.84 (95% CI 3.37-4.36), and 3.75 (95% CI 2.85-4.83) for unspecified glomerulonephritis. The discordant familial risks were high. The risk was increased for any type of glomerulonephritis when family history of any glomerulonephritis was presented; SIR was 2.92 (95% CI 2.72-3.14),
(Table 26).

Table 26.
Concordant and discordant familial risks (parent and/or full-sibling) of glomerulonephritis.

		Males				Females				All			
Disease in relative*	Subtype of glomerular diseases in cases	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Acute glomerulonephritis	Acute	50	4.25	3.15	5.60	17	2.43	1.41	3.90	67	3.57	2.77	4.53
	Chronic	31	1.80	1.23	2.56	19	1.86	1.12	2.91	50	1.83	1.36	2.41
	Unspecified	19	2.28	1.37	3.56	8	1.22	0.52	2.41	27	1.81	1.19	2.64
	All	100	2.68	2.18	3.26	44	1.85	1.34	2.49	144	2.36	1.99	2.78
Chronic glomerulonephritis	Acute	50	2.10	1.56	2.77	33	2.39	1.65	3.36	83	2.21	1.76	2.74
	Chronic	149	3.76	3.18	4.41	90	3.97	3.19	4.88	239	3.84	3.37	4.36
	Unspecified	64	3.58	2.75	4.57	40	2.92	2.09	3.98	104	3.29	2.69	3.99
	All	263	3.23	2.85	3.65	163	3.25	2.77	3.79	426	3.24	2.94	3.56
Unspecified glomerulonephritis	Acute	15	1.26	0.70	2.08	7	1.05	0.42	2.17	22	1.18	0.74	1.79
	Chronic	60	3.12	2.38	4.02	39	3.69	2.63	5.05	99	3.32	2.70	4.05
	Unspecified	37	4.09	2.88	5.64	22	3.28	2.05	4.97	59	3.75	2.85	4.83
	All	112	2.78	2.29	3.35	68	2.84	2.21	3.60	180	2.81	2.41	3.25
All	Acute	115	2.42	2.00	2.90	57	2.08	1.57	2.69	172	2.29	1.96	2.66
	Chronic	240	3.16	2.77	3.58	148	3.41	2.88	4.01	388	3.25	2.93	3.59
	Unspecified	120	3.40	2.82	4.07	70	2.60	2.02	3.28	190	3.05	2.63	3.52
	All	475	2.99	2.73	3.27	275	2.81	2.49	3.16	750	2.92	2.72	3.14

Bold type: 95% CI does not include 1.00.
O = observed number of cases; SIR = standardised incidence ratio; CI = confidence interval
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status. *Only individuals with at least one sibling were included in the analysis.

Multiplex families

We calculated the familial SIRs for glomerulonephritis based on number and type of probands, Table 27. Individuals with one affected parent had SIR=2.54 (95% CI, 2.31-2.78). When both parents were affected the SIR for glomerulonephritis was 6.40 (95% CI, 1.67-16.55). The SIR increased to 209.83 (95% CI, 150.51-284.87) when at least one parent and one full-sibling were affected. Individuals with one affected full-sibling had SIR=3.24 (95% CI, 2.93-3.58), and 263.16 (95% CI 173.25-383.35) for those with two affected full-siblings (Table 27).

Table 27.
Multiplex families. Familial risk of glomerulonephritis according to number of affected relatives.

	Males				Females				All			
Affected relatives	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Parental history	283	2.48	2.20	2.78	194	2.66	2.30	3.06	477	2.55	2.33	2.79
One parent	280	2.46	2.18	2.77	193	2.65	2.29	3.06	473	2.54	2.31	2.78
Both parents	3	7.51	1.42	22.22	1	4.44	0.00	25.47	4	6.40	1.67	16.55
Parent and/or sibling history*	475	2.99	2.73	3.27	275	2.81	2.49	3.16	750	2.92	2.72	3.14
Parent without sibling history	196	2.38	2.06	2.74	129	2.50	2.09	2.97	325	2.43	2.17	2.71
Parent with one or more sibling	28	216.22	143.54	312.86	13	197.27	104.61	338.30	41	209.83	150.51	284.87
Sibling history*	279	3.61	3.20	4.06	146	3.12	2.64	3.67	425	3.42	3.11	3.77
One sibling	267	3.49	3.08	3.93	131	2.84	2.37	3.37	398	3.24	2.93	3.58
Two or more affected siblings	12	237.62	122.19	416.38	15	287.91	160.64	476.02	27	263.16	173.25	383.35
Bold type: 95% CI does not include 1.00.												

O: observed cases; SIR: standardised incidence ratios; CI: confidence intervals.
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status. *Only individuals with at least one sibling were included in the analysis.

Testing for shared non-genetic familial contribution

Two types of tests were performed to study the extent of environmental sharing that contributed to the observed familial aggregation of glomerulonephritis. Familial risks were calculated for spouses diagnosed with glomerulonephritis (Table 24). The familial risks of any glomerulonephritis (acute-, chronic-, and unspecified glomerulonephritis) was modestly increased in spouses among males and females with SIR=1.53 (95% CI 1.33-1.75). Secondly, we calculated the SIRs for full-sibling pairs (sib-pairs) according to age difference (Table 28). Siblings with a difference in age of less than five years had an SIR of 3.62 (95% CI 3.20-4.08) compared with 2.63 (95% CI 2.19-3.13) for those with a difference of at least five years (table 28). Familial risks among siblings with an age difference of less than five years had highest familial risks for chronic, unspecified and acute glomerulonephritis, although the confidence intervals overlapped.

Table 28.
Familial risk of glomerulonephritis in sib-pairs (full-siblings) by age difference.

		≤ 5 years				> 5 years			
Sex	Subtype of glomerular diseases	O	SIR	95% CI		O	SIR	95% CI	
Males	Acute	49	3.76	2.78	4.97	17	1.97	1.14	3.15
	Chronic	84	3.61	2.88	4.47	51	3.41	2.54	4.49
	Unspecified	46	4.53	3.32	6.05	20	2.90	1.77	4.49
	All	179	3.85	3.31	4.46	88	2.89	2.32	3.56
Females	Acute	20	2.69	1.64	4.16	11	2.31	1.15	4.15
	Chronic	51	3.90	2.90	5.13	20	2.38	1.45	3.69
	Unspecified	20	2.61	1.59	4.03	9	1.79	0.81	3.40
	All	91	3.23	2.60	3.96	40	2.20	1.57	3.00
All	Acute	69	3.37	2.62	4.27	28	2.09	1.39	3.02
	Chronic	135	3.71	3.11	4.40	71	3.04	2.38	3.84
	Unspecified	66	3.70	2.86	4.71	29	2.43	1.63	3.49
	All	270	3.62	3.20	4.08	128	2.63	2.19	3.13

Bold type: 95% CI does not include 1.00.
O = observed number of cases; SIR = standardised incidence ratio; CI = confidence interval
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status.

Supplementary analyse of biopsied cases of glomerulonephritis

Including only ICD-10 codes for patients who were biopsied or autopsied with a diagnosis of glomerular disease was performed to test the validity of our results (Table 29). The ICD-10 codes N00-N07 was used in combination with subcodes 0-8. The subcodes 0-8 are only allowed to be used if the patient has been biopsied or autopsied. Few cases were observed but the familial risks were even higher with this definition of histologically verified glomerulonephritis. This analyse was not included in paper III.

Table 29.
Family risks (parent or sibling history) of biopsied glomerulonephritis patients with ICD-10 codes N00-N07 in combination with subcode 0-8 (1997-2012).

	Observed number of cases	SIR	95% CI	
Men	61	3.94	3.01	5.06
Women	62	5.76	4.42	7.39
All	123	4.69	3.90	5.59

Population characteristics study IV

During the study period (1964-2012), a total of 971 individuals were diagnosed with ESRD (Table 30). ESRD was defined as dialysis or kidney transplantation treated ESRD (Table 3). The prevalence for ESRD during the whole study period was 0.6%. Table 30 shows the characteristics for adopted offspring and their biological and adoptive parents: i.e. gender, age at end of follow-up, birth year, educational attainments, cases with ESRD, sex of ESRD cases, and age at ESRD diagnosis.

Table 30.
Descriptive statistics of the study population (n=160912) that constitutes Swedish-born adoptees between 1945 and 1995 and their adoptive and biological parents.

	Adopted offspring (n=37486)	Adoptive parents (n=64139)	Biological parents (n=59287)
Gender, females, n (%)	18 220 (48.60)	29 219 (45.56)	35 743 (60.29)
Median age at end of follow up, years (Q1-Q3)	51 (45 – 59)	78 (69 – 85)	69 (61 – 77)
Birth year, mean (SD)	1961 (10)	1927 (13)	1936 (12)
Birth year, median (Q1-Q3)	1961 (1953-1966)	1925 (1917-1936)	1937 (1928-1945)
Birth year, range (maximum-minimum)	1945-1995	1883-1979	1877-1980
High education, >12 years, n (%)	10 731 (28.63)	9 552 (14.89)	5 283 (8.91)
ESRD cases, n (%)	111 (0.30)	463 (0.72)	397 (0.67)*
Sex of ESRD cases, females, n (%)	47 (0.13)	175 (0.27)	214 (0.36)
Median age at ESRD diagnosis, years (Q1-Q3)	45 (37 – 56)	71 (60 – 77)	66 (57 -73)

SD=Standard deviation, Q1-Q3=first quartile- third quartile= IQR=interquartile range,
*One adopted offspring had two biological parents with ESRD.

The age distribution at time for ESRD in adoptees is presented in Figure 6. The adoptive parents with median age of 78 years (Interquartile range=IQR 69 – 85 years) were older than biological parents with a median age of 69 years (IQR=61 – 77 years) at end of follow-up. Table 30 shows that the median birth year of adoptees was 1961 (IQR, 1953 – 1966), for biological parents it was 1937 (IQR, 1928 – 1945), while it was 1925 (IQR, 1917 – 1936) for adoptive parents. Diabetes mellitus, hypertension, glomerulonephritis, and mortality were more common among study participants with ESRD compared to among those without ESRD (Table 31). Comorbidities were defined by ICD codes according to Table 32.

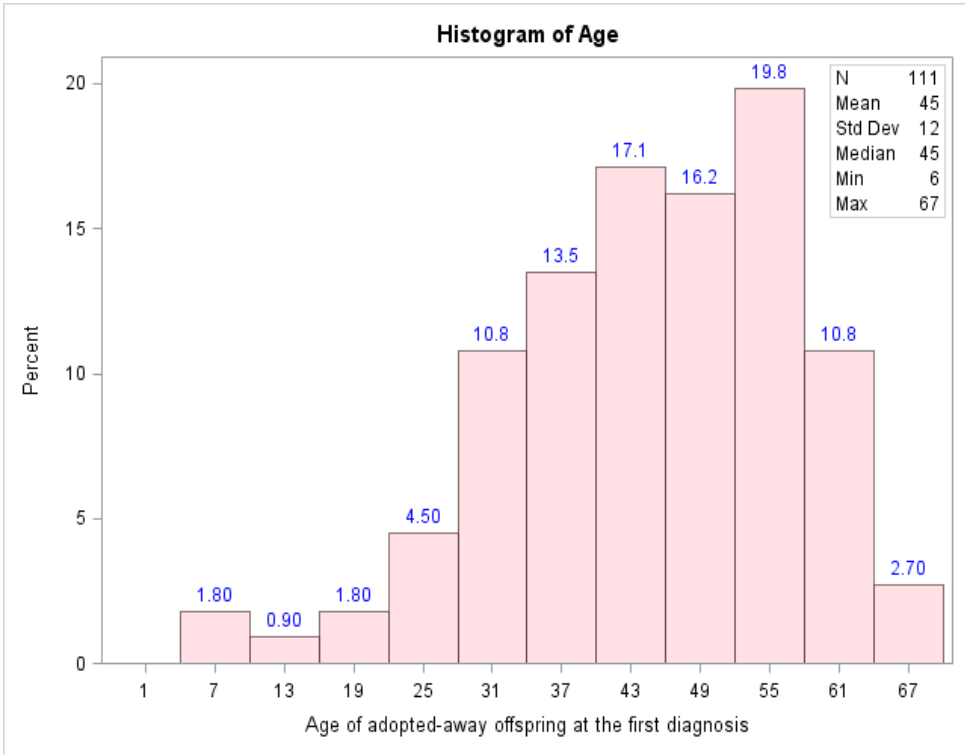


Figure 6.
Age distribution for Swedish-born (1945-1995) adoptees at first time diagnosis of end- stage renal disease (ESRD).

Table 31.
Prevalence of diabetes mellitus, hypertension, glomerulonephritis, and mortality among study participants with and without End Stage Renal Disease (ESRD) any time during follow-up 1964- 2012.

	No ESRD	ESRD	P-value*
Adoptees	(n = 37 375)	(n = 111)	
Diabetes mellitus	1 800 (4.82 %)	56 (50.45%)	<0.0001
Hypertension	3 552 (9.50 %)	77 (69.37%)	<0.0001
Glomerulonephritis	150 (0.40 %)	25 (22.52%)	<0.0001
Mortality	2033 (5.44%)	39 (35.14%)	<0.0001
Biological parents	(n = 58 890)	(n = 397)**	
Diabetes mellitus	7 985 (13.56 %)	181 (45.59 %)	<0.0001
Hypertension	14 814 (25.16 %)	274 (69.02 %)	<0.0001
Glomerulonephritis	254 (0.43%)	82 (20.65 %)	<0.0001
Mortality	27 209 (46.20%)	316 (79.60%)	<0.0001
Adoptive parents	(n = 63 676)	(n = 463)	
Diabetes mellitus	8 483(13.32 %)	161 (34.77 %)	<0.0001
Hypertension	17 631(27.69 %)	317 (68.47 %)	<0.0001
Glomerulonephritis	297 (0.47%)	98 (21.17 %)	<0.0001
Mortality	37 766 (59.31%)	378 (81.64%)	<0.0001

*Both Fisher exact test and Chi square test. **One adopted offspring had two biological parents with ESRD.

Table 32.
Diabetes mellitus, hypertension, and glomerulonephritis (all main and secondary diagnosis among cases) were defined by ICD (International classification of diseases) codes any time during follow-up 1964-2012.

	ICD-10	ICD-9	ICD-8	ICD-7
Glomerulonephritis	N00,N01, N03, N05	580, 582, 583	580, 582, 583	590, 592, 593
Hypertension	I10–I15	401–405	400-404	440-447
Diabetes mellitus	E10–E14	250	250	260

Study results

Cohort design

The ORs with 95% confidence Interval (CI) in the cohort design are shown in Table 33. In the crude model (model 1), the OR for ESRD in adoptees of affected biological parents was increased; OR was 6.40 (95% CI, 2.96 – 13.85). The OR in the adjusted model (model 2) was also significantly increased (OR=6.41 [95% CI, 2.96 – 13.89]). The estimated OR for ESRD in adoptees with an affected adoptive parent was not statistically significant in the crude model (OR 2.23; 95% CI, 0.71 – 7.05) or in the adjusted model (OR 2.40; 95% CI 0.76 – 7.60). The Kaplan-Meier analysis (Figure 7) compares the ESRD-free survival between adoptees with and without an affected biological parent with those without an affected biological parent (Akrawi et al, 2017). The Logrank test (p-value < 0.0001) indicates that the differences between the groups are statistically significant. Using Cox regression, similar results were obtained as using logistic regression (Table 34): model 1 HR=6.28 (95% CI 2.92-13.50); model 2 HR=6.08 (95% CI 2.83-13.08); model 3 HR=2.21 (95% CI 0.70-6.95); and HR=2.31 (95% CI 0.73-7.29). The estimated

Cumulative Incidence Functions (CIF) for ESRD comparing adoptees with affected (ESRD) biological parents with those without affected biological parents is shown in Figure 8; according to Gray´s test (P-value <0.0001). The CIF of ESRD is significantly different between adoptees with and without an affected parent.

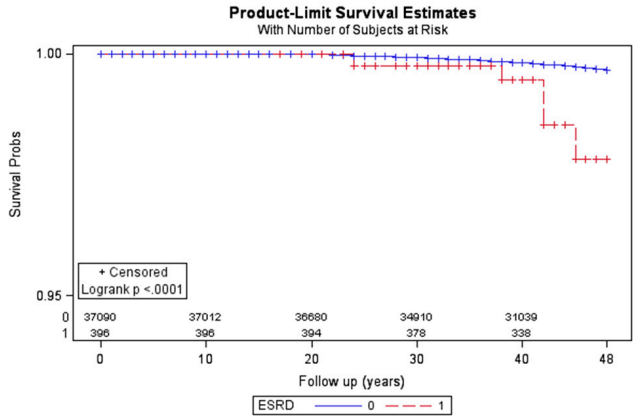


Figure 7
ESRD-free survival curves. Kaplan- Meier analysis comparing adoptees with affected (ESRD) biological parents with unaffected biological parents. The log-rank test (*p* value <0.0001) indicates that differences between the groups are statistically significant. ESRD, end-stage renal disease.

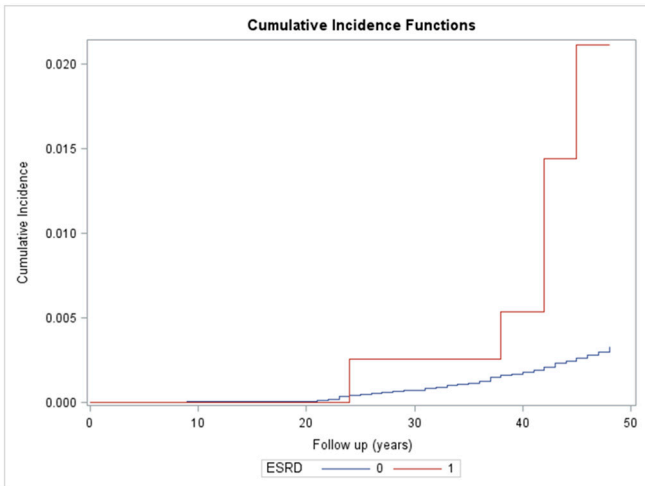


Figure 8.
The estimated Cumulative Incidence Functions (CIF) for ESRD (end stage renal disease) comparing adoptees with affected (ESRD) biological parents with those without affected biological parents. According to Gray´s test (P-value <0.0001). The CIF of ESRD is significantly different between adoptees with and without an affected parent.

Table 33.
Results for the cohort study. Odds ratios (ORs) for ESRD (end-stage renal disease) among Swedish-born adoptees with an affected biological (or adoptive parent) compared with those without an affected biological (or adoptive) parent.

	Biological parents		Adoptive parents	
Risk factors	Model 1[+]	Model 2[#]	Model 3[+]	Model 4[#]
ESRD (in parents)	6.40 (2.96 – 13.85)	6.41 (2.96 – 13.89)	2.23 (0.71 – 7.05)	2.40 (0.76 – 7.60)
Year of birth	0.96 (0.94 – 0.98)	0.96 (0.94 – 0.98)	0.96 (0.94 – 0.98)	0.96 (0.94 – 0.98)
Sex (reference male)	0.78 (0.53 – 1.13)	0.81 (0.55 – 1.18)	0.78 (0.53 – 1.13)	0.81 (0.56 – 1.19)
County	1.01 (0.98 – 1.03)	1.01 (0.98 – 1.03)	1.01 (0.98 – 1.03)	1.01 (0.98 – 1.03)
Education	0.71 (0.55 – 0.91)	0.76 (0.59 – 0.98)	0.71 (0.55 – 0.91)	0.75 (0.59 – 0.97)

[+]Crude model=Univariate model for each variable=Model 1 and Model 3, [#]Multivariate model=Model 2 and Model 4 (all variables included in the model).

Table 34.
Results for the cohort study. Hazard ratios (HRs) for ESRD (end stage renal disease) among Swedish born adoptees with an affected biological (or adoptive parent) compared with those without and affected biological (or adoptive) parent.

	Biological parents		Adoptive parents	
Risk factors	Model 1[+]	Model 2[#]	Model 3[+]	Model 4[#]
ESRD	6.28 (2.92 – 13.50)	6.08 (2.83 – 13.08)	2.21 (0.70 – 6.95)	2.31 (0.73 – 7.29)
Year of birth	0.98 (0.95 – 1.00)	0.98 (0.96 – 1.00)	0.98 (0.95 – 1.00)	0.98 (0.96 – 1.00)
Sex (reference male)	0.77 (0.53 – 1.13)	0.82 (0.56 – 1.20)	0.77 (0.53 – 1.13)	0.82 (0.56 – 1.20)
County	1.01 (0.98 – 1.03)	1.00 (0.98 – 1.03)	1.01 (0.98 – 1.03)	1.00 (0.98 – 1.03)
Education	0.63 (0.48 – 0.82)	0.66 (0.50 – 0.87)	0.63 (0.48 – 0.82)	0.65 (0.50 – 0.86)

[+]Crude model=Univariate model for each variable=Model 1 and Model 3, [#]Multivariate model=Model 2 and Model 4 (all variables included in the model).

Case-Control design

The results of the case-control design are presented in Table 35. ESRD in the adoptees was significantly associated with ESRD in biological parents with an OR of 6.00 (95% CI, 1.83 – 19.60) in adoptees with an affected biological parent. ESRD in an adoptive parent was not significantly associated with ESRD in adoptees, OR= 1.25 (95% CI, 0.14 – 11.18). The estimates in the case–control design (Table 35) are not to a major degree different from the cohort design presented in Table 33 and Table 34.

Table 35.
Results for the matched case control study (1:5). Odds ratios (OR:s) for ESRD end stage renal disease) among adoptees with an affected biological or adoptive parent.

	OR (95% CI)
OR:s for ESRD in adoptees with an affected biological parent*	6.00 (1.83 – 19.66)
OR:s for ESRD in adoptees with an affected adoptive parent*	1.25 (0.14 – 11.18)

Data are presented as OR (95 % CI=confidence interval). *Cases (n = 86) and controls (n = 430).

Heritability

Heritability (h^2 ± standard error) for ESRD was determined with Falconer's regression (Falconer, 1965). Heritability (h^2) was 59.5 ± 18.2 %. The heritability was also calculated in the case-control design with a range of different estimates of the prevalence of ESRD (Table 36) (Frisell et al, 2013). The heritability varied from 40% in a population with 0.01% prevalence to 67% in a population with 2% prevalence. With a prevalence of 0.60% (Table 30), as in the present population, the heritability was 57%, which is similar to what was obtained using Falconer's regression.

Table 36.
Heritability (h^2) of ESRD based on estimated population prevalence and tetrachoric correlation in case-control study according to Frisell et al.

Exposed cases	Unexposed cases	OR	Prevalence	Tetrachoric correlation	Heritability
6	80	6.00	0.01	0.20	40%
6	80	6.00	0.05	0.226	45%
6	80	6.00	0.1	0.24	48%
6	80	6.00	0.5	0.28	56%
6	80	6.00	1.0	0.306	61%
6	80	6.00	1.5	0.32	64%
6	80	6.00	2.0	0.334	67%

Heritability (h2)= the proportion of variance that is due to hereditary factors

Sensitivity Analysis

Sensitivity analyses with both adoptive parents known were performed in order to determine the robustness of results and to assess the effect of lack of information about adoptive child status (did not grow up with one of their biological parents). In Tables 37 and 38 the results are shown for the Cohort and Case-Control studies. Including only adoptees with both adoptive parents identified, even higher familial risks were found.

Table 37.
Odds ratios (ORs) determined with logistic regression for ESRD in adoptees with an affected biological or adoptive parent (Cohort design). Only adoptees with both adoptive parents known were included.

	Biological parents	Adoptive parents
*Variables	Model 3	Model 4
ESRD (in biological parent)	7.90 (3.40 –18.32)	
ESRD (in adoptive parent)		1.95 (0.48 – 8.00)
Year of birth	0.96 (0.93 – 0.98)	0.96 (0.92 – 0.98)
Sex (male reference)	0.75 (0. 48–1.16)	0.74 (0. 48–1.16)
County	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)
Education	0.76 (0.57 – 1.02)	0.76 (0.57 – 1.01)

Model 3: adjusted model; Model 2: adjusted model. *All variables are about adoptees' status.

Table 38.
Results for the matched case control study (1:5). Odds ratios (OR:s) for ESRD among adoptees with an affected biological or adoptive parent. Only adoptees with both adoptive parents known were included.

£OR:s for ESRD in adoptees with an affected biological parent	8.33 (1.99 – 34.87)
*OR:s for ESRD in adoptees with an affected adoptive parent	1.50 (0.14 – 16.54)

Data are presented as OR (95% CI=confidence interval).
£Case (n = 79) and controls (n = 395).
*Due to few observations with 1:5 matching method we performed 1:3. Case (n = 72) and controls (n = 216).

Chapter VII.

Discussion

General discussion of the results

Neighbourhood deprivation and risk of ESRD

This thesis is comprised of four publications; all of the publications are based on a nationwide setting. In **Paper I** an association between neighbourhood deprivation (contextual level) and ESRD was found. This association remained even after adjustment for individual-level sociodemographic factors and comorbidities (compositional level). The recalculation of risk estimation was similar to the more severe phenotype of ESRD used in paper IV. The ICC was low indicating that disease neighbourhood deprivation (contextual effects) contributes only little to the total variance of ESRD in the Swedish population. This is in-line with a critical review by Pickett & Pearl (2001) who found a consistent compositional effect but also a fairly consistent but more modest contextual effect on health. Though many studies have found an association between socioeconomic disparities, both compositional and contextual, only a few studies have adjusted for individual-level SES, i.e. multilevel modelling (Merkin et al, 2005; McClellan et al, 2010; Merkin et al, 2007; Shoham et al, 2008). These studies that take both compositional and contextual factors into account have shown diverging results. The present study suggests that this might be because the contextual factors have a small contribution to ESRD with only slightly increased odds ratios and low ICC. Due to the low effect size, neighbourhood studies for ESRD studies are therefore more sensitive to study size (statistical power), random findings, and methodological flaws. According to Bradford Hills, the first criteria for causality, i.e. the larger effect size (strength), the higher the probability for a causal association. Moreover, Hills second criteria consistency (reproducibility) between study not fulfilled for neighbourhood deprivation and ESRD or CKD. This argues against any important causal association between neighbourhood deprivation and ESRD. It appears that compositional factors are more important at least for ESRD. Otherwise, several possible mechanisms explaining the association between socioeconomic disparities and disease have been suggested. Psychological stress could be one mediator due to unsafe environments, vandalism, isolation/alienation and violent

crime in marginalised neighbourhoods, (Holden et al, 2010; Sundquist K et al 2006). Moreover, the variation in sociocultural norms regarding diet, smoking, and physical activity between neighbourhoods could affect the health of residents and additional risk of disease, (Ejerblad et al, 2004). Cardiovascular risk factors including physical inactivity, obesity and smoking were more common among individuals living in more deprived neighbourhoods according to a Swedish study which gives an account of possible explanations concerning increased disease risk, (Sundquist et al, 1999).

Familial risks and kidney failure

Paper II was the first nationwide follow-up study of familial risks of kidney failure for both chronic and acute forms. Paper II evaluated the familial risk of chronic, acute and unspecified kidney (not acute or chronic) failure among offspring/siblings of affected individuals. Previous studies have shown that familial factors are important for progressive chronic kidney failure, (Ferguson et al, 1988; Freeman BI et al, 1993; O´Dea DF et al, 1998; McCellan W et al, 2007; Freedman BI et al, 1997). Paper II confirms that familial factors are important for chronic kidney failure in nationwide follow-up data. The results show that familial factors are important for chronic kidney failure in both male and females of all ages except <10 years. The familial risks for chronic kidney failure were highest at ages 10-19 years. The results also show that familial factors and most likely genetic factors are less important in acute kidney failure. Acute renal failure is instead often related to old age, multi-morbidity, and multiple drugs (Li et al, 2013). Etiological factors include pre-renal injury that contribute to reduced renal perfusion. Precipitating events may also be iatrogenic such as hypotension during anaesthesia and surgery.

In genome wide association studies, it has been found that risk alleles added little to the prediction of CKD (O´Seaghdha & Fox, 2011; Köttgen et al, 2009; Köttgen et al, 2010). Both genetic and environmental familial factors could predispose individuals for chronic kidney failure. In paper II age difference between siblings had little influence on chronic kidney failure, which supports a genetic contribution. With the hypothesis that shared familial environmental factors are important we should expect higher risks for siblings with smaller age differences. The higher familial risk observed for the more severe phenotype dialysis and transplantation treated ESRD also suggests a genetic cause. In complex traits, it is common that genetic factors are more involved in the most severe phenotypes of a disease (Lander & Schork, 1994). Our findings suggest that it could be worthwhile to pursue further studies aiming to identify novel gene variants causing CKD and ESRD in the Swedish population. Moreover, family history of CKD or ESRD

could be a clinical risk marker even in the absence of known genetic gene variants for CKD and ESRD.

Familial risks and glomerulonephritis

Paper III was the first nationwide follow-up study of familial risks of glomerulonephritis (acute, chronic and unspecified) among offspring/full-siblings and examined the spouses of affected individuals. Results in the third study indicate that family history of glomerulonephritis is a strong predictor for glomerulonephritis in Sweden. Previously, causative mutations have been identified in patients with glomerular disease (Hildebrandt, 2010). High familial risks were observed among multiplex families in paper III, which suggests a strong genetic contribution. The results indicate that the familial concordant risks were high for chronic glomerulonephritis and they were lower for acute and unspecified glomerulonephritis. Paper III also indicates that familial factors are of importance in acute, chronic and unspecified glomerulonephritis. This is analogous to previous studies that have recognised that glomerulonephritis is aggregated in families (Rambausek et al, 1993; Izzy et al, 2006; Scolari et al, 1992).

To account for the adult shared environmental contribution to glomerulonephritis, the risk of glomerulonephritis among spouses was determined. Spouse risks were low compared to familial risks in first -degree relatives. The spouse risk was much lower than the sibling or parent-offspring risks thus suggesting that the familial risk in siblings and offspring is more related to genetic than household environmental factors. However, there was a significantly increased spouse risk that could be related to shared familial environmental exposure, diet, alcohol, smoking and exercise habits (Lawlor & Mishra, 2009). Shared exposure for infections could theoretically also be of importance.

Higher familial risks for glomerulonephritis in siblings with a difference in age of less than five years were observed, which further suggests a partial non-genetic effect of shared familial environments. The exposure for environmental factors such as infections, food and certain chemicals in different generations may vary (Segelmark M & Hellmark T, 2010). However, the very high risk in multiplex families indicates a strong genetic cause (Burton et al, 2005). Another possible hypothesis for the tendency for higher sibling than parent-offspring risk could be due to recessive genes (Hildebrandt, 2010).

Heritability and ESRD

In **Paper IV** was observed a high heritability of ESRD indicating that genetic factors are important risk factors causing ESRD in Sweden. The results confirm the finding of previous studies showing strong familial clustering of ESRD (Freedman & Robinson, 2014; Ferguson et al, 1988; Freedman et al, 1993; Freedman et al, 1997). Paper III, which is the first adoption study for ESRD, extends on previous studies. The adoption design indicates that genetic factors, and not only shared familial environmental factors, are important in the familial transmission of ESRD. Previously, a twin study has shown a heritability of 50% for estimated glomerular filtration rate (eGFR) (Raggi et al, 2010). In another twin study, Arpegård et al (2015) estimated the heritability of Cystatin C (60%) and creatinine (59%). No twin study that formally determines heritability (h^2) of ESRD has been published. Our fourth study is the first one estimating the heritability of ESRD. The high heritability for ESRD in the present study is similar to the heritability estimated for different measures of kidney functions (Raggi et al, 2010; Arpegård et al, 2015). It is not likely that the present results overestimate the heritability of ESRD because severe phenotypes are often more heritable than less severe phenotypes such as measure of kidney function in a cohort of twins. This explains the lower heritability study of ESRD from Taiwan that included patients on dialysis but also less severe cases with CKD (International classification of disease 9 [ICD-9] code 585) heritability was 31.1% (Wu et al, 2017). The FFR was 2.46 (95% CI, 2.32-2.62).

The high heritability of ESRD suggests that gene hunt studies for common genetic variants may be worthwhile. The results are analogous with the recent rapid progression of genome wide association studies (GWAS) of various kidney traits and disorders (Wuttke & Köttgen, 2016). Genetic studies, used to investigate traits that define chronic kidney disease (CKD), such as eGFR or urinary albumin/creatinine ratio, have identified more than 50 associated genomic regions (Arpegård et al, 2015). Most interestingly, genomic regions identified in GWAS of CKD-defining traits partly overlap with causal genes for monogenic kidney diseases. GWAS research on kidney function traits may therefore provide knowledge about the more severe forms of kidney diseases (Wuttke & Köttgen, 2016). However, until all genetic variants associated with kidney disease and ESRD are discovered, family history will continue to be important. This study shows that shared genes make a strong contribution to familial risks and that family history of ESRD may signal an increased genetic risk of ESRD.

Strengths and limitations

Paper I

A limitation to consider in studies of neighbourhood effects on health is selective residential mobility—the tendency of individuals to move to neighbourhoods that have characteristics that match their individual characteristics (for example, the tendency of individuals with low SES to move to low-SES neighbourhoods)—can cause compositional neighbourhood differences. However, we adjusted for individual-level SES, which improved our ability to differentiate between compositional and contextual effects on ESRD. No information on data about smoking and body mass index in the study population exists. Although we adjusted for diagnoses of chronic lower respiratory diseases and obesity, residual bias is likely to exist for several individual factors.

Strengths of paper one are that the large cohort included practically all patients aged 20-69 years with ESRD diagnoses in the Swedish Hospital Discharge Register and Outpatient Register. This increases the generalisability of the results. Another strength is the use of personal identification numbers, which made it possible to follow individuals in different registers. Data in the Swedish Hospital Discharge Register are almost complete. In 2001, identification numbers were 99.6% complete and the main diagnosis was missing for only 0.9% of hospitalisations (Ludvigsson et al, 2009). A further strength is the high validity of the Hospital Discharge Register (Ludvigsson et al 2011; Zöller, 2013). About 85-95% of most diagnoses have been shown to be correct (Ludvigsson et al, 2011; Zöller, 2013). A limitation is that there has been no specific validation study for ESRD. However, validity for surgery procedure codes is generally high (Ludvigsson et al, 2011). This is exemplified by the fact that for kidney transplantation there is 95% agreement between the Swedish Hospital Discharge Register and the Swedish Renal Registry (Socialstyrelsen, 2012). The Swedish Renal Registry is a voluntary quality registry for patients with chronic renal failure in Sweden, and is maintained by the Swedish Renal Medical Association and the Swedish Transplantation Society. However, for the diagnosis of ESRD in patients without dialysis or transplantation the agreement is lower. For the diagnosis codes N18.4 (stage 4 CKD) and N18.5 (stage 5 CKD), agreement with the Swedish Renal Registry is only 36%, with coverage of 61% (Socialstyrelsen, 2013). This is probably due to the use of N18.9 (unspecified renal failure) instead of N18.4 and N18.5 (Socialstyrelsen, 2013). However, with regard to neighbourhood deprivation, this possible underreporting of N18.4 and N18.5 in the Swedish Hospital Discharge Register is most likely a source of non-differential bias. Moreover, in the present study only the N18.5 code (stage 5 CKD) was used; N18.4 (stage 4 CKD) was not used. Thus, the present study mainly reflects

patients with stage 5 CKD, who are treated with dialysis or renal transplantation. This was confirmed by using the same definition of ESRD as in paper IV, i.e. chronic dialysis and kidney transplantation treated ESRD.

Paper II

Strengths of the second study include complete nationwide coverage from 1987 in a country with high standards of diagnosis, with diagnoses often being made by specialists during extended examinations in clinics. The Swedish hospital discharge register contains no information about diagnostic procedures, which however is a limitation. Moreover, the validity of ICD codes for kidney disease has not been reported. However, the Swedish hospital discharge register has been extensively validated and its overall diagnostic validity is around 85-95% for many diagnoses (Ludvigsson et al, 2011). A limitation was the inclusion of asymptomatic early stages of renal failure. Recalculation using the same definition of ESRD as in paper IV, i.e. chronic dialysis and kidney transplantation treated ESRD gave even high FRR.

A likely non-differential bias regarding familial risks is that cases in probands and relatives before 1987 are unknown. Moreover, the number of comorbidities is rather low, possible due to that diagnoses made in primary health are not included. No nationwide primary health care register existed in Sweden at the time of the study.

Another important strength is the lack of selection and recall bias. The Swedish Multi-generation register and the Swedish hospital discharge register are validated data sources that have been proven to be reliable in the study of many diseases (Rosen & Hakulinen, 2005; Ekbom, 2011).

Paper III

The nationwide setting of study III is a strength. This is the first nationwide study evaluating the familial risks of acute, chronic and unspecified glomerulonephritis. Moreover, the study was based on national registers used by Swedish specialists and is free from recall bias. The study design also minimised selection bias, which is another strength of this study. The data reflects the total impact of familial risks of glomerulonephritis in the whole population of Sweden. One limitation in study III is that in the Swedish hospital discharge register there is no information about the diagnostic procedure. Moreover, using ICD-codes is limited to acute-, chronic and unspecified glomerulonephritis which makes it possible that some patients with glomerulonephritis related to isolated haematuria, isolated proteinuria, and nephrotic syndrome were missed at least for ICD-10 codes. Another limitation is

the lack of information about biopsies in ICD-7, ICD-8, and ICD-9. We therefore limited the inclusion of patients with a diagnosis of glomerulonephritis and no other more unspecific related clinical diagnosis although some cases could be missed. Moreover, cases with ICD codes related to glomerular disease in vasculitis patients were not included. We know from previously evaluations that the Swedish hospital discharge registers have extensively been validated by Ludvigsson et al (2011), and the validity is around 85-95% for most diseases. However, kidney diseases including glomerulonephritis have not been validated, which is a limitation. A supplementary analyse with inclusion of all biopsied or autopsied patients with a histological diagnosis of glomerulonephritis with ICD-10 codes N00-N07 (and subcodes 0-8) showed even higher familial risk of 4.69 (95% CI 3.90-5.59). Thus, our results may underestimate the familial risks of glomerulonephritis due to inclusion of non-biopsied patients. The non-biopsied cases probably are less severe or in some cases even misdiagnosed. In genetics cases with a more severe phenotype often have a stronger genetic predisposition (Lander & Schork, 1994). The possible regional diagnostic accuracy could be another possible bias; to minimise it the analysis was adjusted for geographic region. A possible non-differential bias is that there is no information about cases in probands and relatives before 1964. Moreover, there is no data on lifestyle related factors, such as body mass-index (BMI), smoking and diet. Such data gathering is unrealistic for the entire national population. Adjustment was instead done for socioeconomic status, which is associated with many lifestyle factors, such as smoking. As in all epidemiological studies residual confounders may exist.

Paper IV

Estimating the heritability of ESRD in an adoption study (paper IV) has not previously been published. Defining the family history of ESRD by NPR-diagnosis and not self-reporting is a strength of the study to avoid recall bias (Zöller, 2013). However, the use of register-based data could be a potential source of error. It is not known how ESRD diagnosis was established. However, using the definition of dialysis or transplantation (i.e. in active uremic care) treated ESRD is likely to secure high validity in the study. There is a high validity of diagnosis in the Swedish hospital register ranging from 85 to 95% for many diagnoses (Ludvigsson, 2011). A strength is that the Swedish NPR concurs regarding ESRD patients in active uremic treatment) with the Swedish Renal Register (SRR) (Schön et al, 2004; Welander et al, 2012). The SRR has been extensively used and, when validated, the authors found that >95% of persons with ESRD were reported to the SRR (Schön et al, 2004; Welander et al, 2012). Registers used in this study are almost complete and have successfully been used to estimate familial risks for a number of diseases (Rosen M, Hakulinen T, 2005; Ekbom A, 2011).

Another limitation is that information about the age at which children were adopted was not available, although it is likely that most adoptions occurred in early childhood (Nordlöf, 2001; Bohman, 1970). The adoption study included only adoptees that were born in Sweden. The generalizability of this study to other populations of non-European origin cannot be concluded.

Chapter VIII.

Conclusion

The present thesis, which is based on four papers (I-IV), shows that familial and hereditary factors are important for the burden of chronic kidney failure, end stage renal disease, and glomerulonephritis in Sweden. In glomerulonephritis, there is also a weaker contribution of shared familial household factors reflected by an increased risk among spouses. The heritability of end stage renal failure is high in the Swedish population. By contrast, the familial and genetic contribution to acute renal failure is weak. Moreover, neighbourhood deprivation (contextual factors) make a small contribution to the burden of end stage renal disease, when compositional factors (individual factors) are taken into account. Thus, compositional (individual) factors are more important than contextual factors for the development of end stage renal disease.

The result of this thesis suggests that family history for CKD, ESRD, and glomerulonephritis might be useful for risk assessment and possible screening for identification and early treatment of individuals at increased risk for CKD, ESRD, and glomerulonephritis in order to slow progression of disease. The importance of hereditary factors in the present thesis suggests that continued gene hunt for novel causes of CKD, ESRD, and glomerulonephritis could be worthwhile. The identification of novel gene variants could lead to not only better risk assessment but also novel treatments for the disease.

Future perspectives

Kidney diseases have been targeted to biomedical research because of their high impact on individual's quality of life and the associated high costs for the society. The difficult consequences of kidney failure for the individuals including chronic dialysis and kidney transplantation call for more attention for these disorders. Observational studies like this, give more attention to the importance of continuous research on kidney disturbances. In this thesis we have shown that neighbourhood deprivation contributes to ESRD only to a minor degree. In contrast, the present thesis shows that chronic kidney failure and glomerulonephritis strongly clusters in families in Sweden. The high heritability of ESRD underlines the importance of additive genetic factors for the development of ESRD in Sweden.

The findings and observations in this thesis suggest that family history of kidney failure and glomerulonephritis could be the starting point for prevention and screening in order to identify individuals at increased risk. This line of research could be further studied in clinical settings. The strong familial clustering of glomerulonephritis and ESRD gives hopes for the future. Hopefully with the rapid advances in molecular biology such as whole genome sequencing and bioinformatics will lead to identification of novel gene loci involved in these disorders. This may lead to novel and specific methods for prevention and treatment of ESRD and glomerulonephritis.

Populärvetenskaplig sammanfattning

Kronisk njursjukdom (chronic kidney disease, CKD) är ett växande problem. Diabetes och hypertoni, två vanliga tillstånd inom primärvården, är de viktigaste orsakerna till CKD. Med njurinsufficiens (njursvikt) avses nedsatt njurfunktion. Njurfunktionen är liktydigt med den glomerulära filtrationshastigheten (GFR). Njurinsufficiensen kan med utgångspunkt från GFR-nivå, indelas i fem stadier, CKD (chronic kidney disease) 1-5. Det står numera klart att en individs risk att utveckla progressiv kronisk njursjukdom beror på en komplex interaktion mellan multipla genetiska och förvärvade faktorer. Familjär aggregation av CKD och ESRD (end stage renal disease) är vanligt. Det är känt att t.ex. att familjära faktorer har betydelse för att utveckla CKD och ERSD vid diabetes. Det saknas emellertid stora nationella studier där familjära risker har karakteriserats i detalj. Den bakomliggande genetiska orsaken är dessutom oftast okänd och det är av värde för bättre prevention att kunna identifiera riskindivider. Årligen får 9693 patienter (Svenska njurregister, Årsrapport 2017) vård på Svenska sjukhus p.g.a. svår njursvikt. Njurtransplantation är en slutgiltig behandling hos 424 patienter årligen (Svenska njurregister, Årsrapport 2017). Njursjukdom orsakar stort lidande och höga kostnader för sjukvården. Bättre prevention, identifikation och behandling av riskfaktorer för planering av framtida aktiv uremivård är därför av stor vikt.

Det första delarbetet avhandlar boendeområdets sociala utsatthets betydelse för terminal njursvikt (ESRD) i Sverige. Flernivå-analys (Multi-level) med logistisk regression användes för att undersöka grannskapets effekt på risken att utveckla svår njursvikt. Boendeområdets sociala utsatthet var en oberoende risk faktor för terminal njursjukdom i Sverige även om dess bidrag till den totala variationen inte var så stor i absoluta tal. Boendeområdets effekt för risken att insjukna i svår njursvikt var oberoende av individuella sociodemografiska variabler och samsjuklighet hos såväl kvinnor som män.

I det andra delarbetet undersöktes familjära risker hos första grads släktingar till njursvikts patienter. Studien är en svensk nationell historisk kohortstudie. Standardiserad incidens ratio (SIR) användes för att räkna ut de familjära riskerna. Den fanns en stark ärftlighet för kronisk njursvikt men endast en svag eller obefintlig ärftlighet för akut njursvikt. Patienter som fått diagnosen ospecificerad njursvikt (d.v.s. njursvikt som inte kunde klassas som akut eller kronisk)

uppvisade en måttlig ärftlighet. Resultaten indikerar att familjära och med största sannolikhet genetiska faktorer är av betydelse för framförallt kronisk njursvikt.

I det tredje delarbetet analyserades familjära risker av akut, kronisk och ospecificerad glomerulonefrit. Med ospecificerad avses glomerulonefrit som inte gick att klassificera som akut eller kronisk. Glomerulonefrit är en vanlig orsak till dialysbehandlad njursvikt. Det finns många studier tidigare som visat på ärftlighet för glomerulonefrit men ingen har publicerat de familjära riskerna i en nationell studie. Studien baserades på det svenska patientregistret och flergenerationsregistret. Förekomst av glomerulonefrit hos en förstagradssläkting är en stark risk faktor för utveckling av glomerulonefrit. Den statistiska metoden som användes var Standardiserad incidens ratio (SIR) som också används i delarbete II.

Det fjärde delarbetet är en adoptionsstudie för att skilja genetiska från familjära miljöeffekter (shared environment) för terminal njursvikt. Studien är en register studie som använde det svenska patientregistret och flergenerationsregistret. Familjära risker bestämdes i relation till biologiska respektive adoptiv föräldrar. Risken att få terminal njursvikt för adopterade barn var kraftigt ökad om deras biologiska föräldrar drabbades av njursvikt. Ingen statistisk säkerställd riskökning noterades om deras adoptiva föräldrar drabbades av njursvikt. Med hjälp av Falconers metod visades att heritabiliteten (ärftligheten) för terminal njursvikt är mycket hög (59.5%), vilket innebär att ärftliga faktorer är viktiga i befolkningen för insjuknande i terminal njursvikt.

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Original Article

End stage renal disease risk and neighbourhood deprivation: A nationwide cohort study in Sweden

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ABSTRACT

Background: Chronic kidney disease has been associated with socioeconomic disparities and neighbourhood deprivation. We aimed to determine whether there is an association between neighbourhood deprivation and end stage renal disease (ESRD), and whether this association is independent of individual-level sociodemographic factors and comorbidities.

Methods: National Swedish data registers were used. The entire Swedish population aged 20–69 years was followed from January 1, 2001 until December 31, 2010. Data were analysed by multilevel logistic regression, with individual-level sociodemographic factors (age, marital status, family income, education level, country of birth, urban/rural status, and mobility) and comorbidities at the first level and neighbourhood deprivation at the second level.

Results: Neighbourhood deprivation was significantly associated with ESRD (age-adjusted odds ratio [OR] 1.45, 95% confidence interval [CI] 1.34–1.56 in men and OR 1.59, 95% CI 1.44–1.75 in women). The ORs for ESRD in men and women living in the most deprived neighbourhoods remained significantly increased when adjusted for age and individual-level sociodemographic factors (OR 1.25, 95% CI 1.15–1.35 in men and OR 1.30, 95% CI 1.17–1.44 in women). In the full model, which took account of sociodemographic factors and comorbidities, the ORs for ESRD remained significantly increased (OR 1.17, 95% CI 1.07–1.27 in men and OR 1.18, 95% CI 1.06–1.31 in women).

Conclusion: Neighbourhood deprivation is independently associated with ESRD in both men and women irrespective of individual-level sociodemographic factors and comorbidities.

1. Introduction

Chronic kidney disease (CKD) is a worldwide health problem associated with poor outcomes, high costs, and increased risk of cardiovascular mortality and morbidity [1]. Factors associated with CKD are old age, diabetes mellitus, hypertension, obesity, cardiovascular disease (CVD), ethnicity, family history, and socioeconomic status (SES) [2,3]. Individual-level SES, such as household income, education level, wealth, and occupation, has been associated with lower levels of glomerular filtration [4–8]. In addition to individual-level SES, neighbourhood-level factors may also increase the risk of CKD [9–16]. However, few studies have determined whether neighbourhood deprivation is a risk factor for end stage renal disease (ESRD), independent of individual-level sociodemographic factors, including SES, and comorbidities. In the Atherosclerosis Risk in Communities (ARIC) study only white men had an independent increased risk of progressive CKD in lower SES neighbourhoods [13]. White women, black women, and black men living in lower SES neighbourhoods had no increased risk of CKD compared to their counterparts in higher SES neighbourhoods [13]. In a study by McClellan et al., household but not community poverty was independently associated with CKD [17]. In US people aged above 65 years a significant association was found between living in a poor neighbourhood and CKD, independent of individual-level SES, lifestyle factors, diabetes, and hypertension [18]. In the ARIC study of life-course socioeconomic conditions, after adjustment for diabetes and hypertension, individual-level SES was independently associated with CKD, but neighbourhood-level SES was not [19].

These studies suggest that the associations of individual-level SES and neighbourhood-level SES with CKD and ESRD are complex. Moreover, it is not clear whether comorbidities influence these associations. We aimed to determine, in a large nationwide study, whether there is an association between neighbourhood deprivation and ESRD, and whether this association is independent of individual-level sociodemographic factors, including SES (age, marital status, family income, education level, country of birth, urban/rural status, and mobility) and comorbidities.

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2. Methods

2.1. Study design

Data used in this study represent information on all individuals registered as residents of Sweden and aged between 20 and 69 years at the start of the follow-up (January 1, 2001). The data included individual-level information on age, sex, education, occupation, geographic region of residence, hospital diagnoses, and dates of hospital admissions in Sweden, as well as date of emigration, and date and cause of death. The data sources were several national Swedish data registers, including the Swedish National Population and Housing Census, the Total Population Register, the Multi-Generation Register, the Swedish Cancer Registry, and the Swedish Hospital Discharge Register and Outpatient Register, and were provided to us by Statistics Sweden (the statistics bureau owned by the Swedish government) and the National Board of Health and Welfare [20–22]. The dataset includes ESRD events for the entire population, as well as information on individual-level SES and neighbourhood-level SES [23–25]. We used the main diagnoses of ESRD recorded in the Hospital Discharge Register and Outpatient Register and surgical codes for renal transplantation and dialysis. Linkages were carried out to national census data to obtain data on individual-level SES and geographical region of residence; to the national Cause of Death Register to obtain date of death; and to the Migration Register to obtain date of immigration or emigration. All linkages were performed using the individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number in order to ensure anonymity. The follow-up period started on January 1, 2001 and proceeded until diagnosis of ESRD, death, emigration, or the end of the study period (December 31, 2010).

2.2. Outcome (dependent) variable

The outcome variable, ESRD, was based on the 10th revision of the International Classification of Diseases (ICD) or the Classification of Surgical Procedures. ESRD was defined as N18.5 (i.e. CKD stage 5), T82.4, Y84.1, Z49, Z94.0, and Z99.2 (ICD-10 codes for ESRD, dialysis or transplantation), and V9211, V9212, V9200, V9531, V9532, V9507, KAS00, KAS10, KAS20, KAS40, KAS50, KAS60, KAS96, KAS97, JAK10, TJA33, TJA35, and TKA20 (surgical codes for transplantation or dialysis). The frequencies of the different diagnoses for ESRD at presentation are shown in Supplementary Table 1.

2.3. Individual-level variables

The individual-level variables were sex, age at the start of the study, marital status, family income, education level, country of birth, urban/rural status, mobility, and comorbidities [23–25].

Sex: male or female.

Age ranged from 20 to 69 years and was used as a continuous variable in the models.

Marital status: individuals were classified as married/cohabitating or never married/widowed/divorced.

Family income by quartile: information on family income in 2001 came from the Total Population Register, which was provided by Statistics Sweden. Income was categorised into quartiles: low income, middle–low income, middle–high income, and high income.

Education level was classified as completion of compulsory school or less ($\leq$9 years), practical high school or some theoretical high school (10–12 years), and theoretical high school and/or college (>12 years).

Country of birth: Born in 1) Sweden (reference), 2) Finland, 3) Western countries, 4) Eastern European countries, 5) Middle Eastern countries, and 6) other countries.

Urban/rural status: residence in large cities (Stockholm, Gothenburg, and Malmö), middle-sized towns, and small towns/rural areas.

Mobility: length of time lived in neighbourhood, categorised as <5 years (moved) or $\geq$5 years (not moved).

Comorbidity was defined as the first diagnosis (main or additional diagnosis) during the follow-up period of: 1) chronic lower respiratory diseases (J40-J49), 2) obesity (E65-E68), 3) alcoholism and alcohol-related liver disease (F10 and K70), 4) hypertension (I10-I15), 5) diabetes mellitus (E10-E14), 6) ischemic heart disease (I20-I25), and 7) acute kidney failure (N17).

2.4. Neighbourhood-level SES

The home addresses of all Swedish individuals have been geocoded to small geographical units that have boundaries defined by homogeneous types of buildings. These neighbourhood areas, called small area market statistics, or SAMS, have an average of 1000 people each and were created by Statistics Sweden. SAMS were used as proxies for neighbourhoods, as in previous research [26,27]. SAMS with fewer than 50 people aged 25–64 were excluded (n = 1053 SAMS), as were individuals whose addresses could not be geocoded to a neighbourhood area (n = 83,230 individuals, 13% of the sample). The final sample included 8372 SAMS.

A summary index was calculated to characterise neighbourhood-level deprivation [28]. The neighbourhood index was based on information on women and men aged 20–64 who lived in the neighbourhood because people in this age group are the most socioeconomically active, that is, as a population group they have a stronger impact on the socioeconomic structure of the neighbourhood than children, younger women and men, and retirees. The neighbourhood index was based on four items: low education level (<10 years of formal education), low income (income from all sources, including that from interest and dividends, defined as less than 50% of the median individual income), unemployment (excluding full-time students, those completing compulsory military service, and early retirees) and receipt of social welfare. The index was categorised into the following three groups (higher scores reflect more deprived neighbourhoods): low neighbourhood deprivation (more than 1 SD below the mean), moderate neighbourhood deprivation (within 1 SD of the mean), and high neighbourhood deprivation (more than 1 SD above the mean) [28].

2.5. Statistical analysis

Age-adjusted cumulative incidence rates were calculated by direct age standardisation using 10-year age groups, with the entire study population of women or men in 2001 as the standard population. Multilevel (hierarchical) logistic regression models with incidence proportions (proportions of adults who became cases among those who entered the study time interval) were used to calculate the outcome variable. Multi-level logistic regression models are a good approximation of Cox proportional hazards models under certain circumstances such as ours (large sample size, low incidence, and risk ratios of moderate size) [29]. The analyses were performed using MLwiN version 2.27. First, a neighbourhood model including only neighbourhood-level deprivation was created to determine the crude odds of ESRD by level of neighbourhood deprivation. A second model included neighbourhood-level deprivation and age; a third model also included the other individual-level sociodemographic variables (added simultaneously to the model). The full model tested whether neighbourhood-level deprivation was significantly associated with ESRD after adjustment for individual-level sociodemographic factors as well as comorbidity [30]. In the Atherosclerosis Risk in Communities (ARIC) study, white men but not women had an independent increased risk of progressive CKD in lower SES neighbourhoods [13]. Men and women were therefore analysed in separate models. Interaction tests (for both men and women) examined whether the effects of neighbourhood-level deprivation on ESRD rates differed across individual-level SES (income and education) categories, that is, they tested for effect modification.

Collinearity was not a problem. There was a low degree of correlation between the factors included in the models.

Random effects: the between-neighbourhood variance was estimated both with and without a random intercept. It was regarded to be significant if it was larger than 1.96 times the standard error.

3. Ethical considerations

The Ethics Committee of Lund University, Sweden approved this study.

4. Results

4.1. Basic population characteristics

The study population consisted of 5,593,516 individuals. Table 1 shows baseline population characteristics in the year 2001. Of the total population, 1,301,351 (23%), 3,370,070 (60%), and 922,095 individuals (17%) lived in low-, moderate-, and high-deprivation neighbourhoods, respectively. During the follow-up period, 12,348 individuals were diagnosed with ESRD. The age-adjusted cumulative incidence rate of ESRD increased from 1.8 per 1000 in neighbourhoods

Table 1
Population characteristics and end stage renal disease (ESRD) by level of neighborhood deprivation: 2001–2010.

	Study population		ESRD events		Incidence of ESRD by level of neighborhood deprivation		
	(N)	(%)	(N)	(%)	Low	Moderate	High
Total population	5,593,516				1,301,351 (23.3%)	3,370,070 (60.2%)	922,095 (16.5%)
ESRD			12,348		1.8	2.3	2.5
Age (years)							
20–29	1,092,948	19.5	712	5.8	0.5	0.7	0.7
30–39	1,264,439	22.6	1520	12.3	0.9	1.3	1.5
40–49	1,163,403	20.8	2385	19.3	1.6	2.1	2.6
50–59	1,241,349	22.2	3950	32.0	2.6	3.2	4.0
60–69	831,377	14.9	3781	30.6	3.7	4.6	5.4
Gender							
Male	2,826,359	50.5	7870	63.7	2.3	2.9	3.1
Female	2,767,157	49.5	4478	36.3	1.3	1.6	1.9
Education level							
≤9 years	1,249,236	22.3	4336	35.1	2.3	2.9	3.0
10–12 years	2,700,091	48.3	5560	45.0	1.9	2.3	2.4
>12 years	1,644,189	29.4	2452	19.9	1.5	1.7	1.7
Marital status							
Married/cohabiting	2,575,915	46.1	6331	51.3	1.7	2.1	2.4
Never married, widowed, or divorced	3,017,601	53.9	6017	48.7	1.9	2.5	2.6
Family income							
Low income	1,399,791	25.0	2781	22.5	2.0	2.5	2.8
Middle–low income	1,400,677	25.0	3489	28.3	2.2	2.6	2.8
Middle–high income	1,396,660	25.0	3348	27.1	2.0	2.3	2.5
High income	1,396,388	25.0	2730	22.1	1.5	1.9	1.8
Country of origin							
Sweden	4,797,837	85.8	10,531	85.3	1.8	2.3	2.5
Finland	163,533	2.9	379	3.1	1.5	1.9	1.8
Western countries	51,828	0.9	119	1.0	1.6	1.8	2.6
Eastern European countries	114,770	2.1	317	2.6	2.7	3.0	2.8
Middle Eastern countries	141,019	2.5	291	2.4	3.4	2.9	3.3
Others	324,529	5.8	711	5.8	1.9	2.4	2.8
Urban/rural status							
Large cities	2,854,538	51.0	6436	52.1	1.8	2.4	2.8
Middle-sized towns	1,852,901	33.1	3974	32.2	1.7	2.2	2.2
Small towns/rural areas	886,077	15.8	1938	15.7	1.7	2.1	2.3
Mobility							
Not moved	3,455,429	61.8	8912	72.2	1.8	2.3	2.5
Moved	2,138,087	38.2	3436	27.8	1.9	2.3	2.5
Chronic lower respiratory disease							
No	5,458,926	97.6	11,659	94.4	1.7	2.2	2.4
Yes	134,590	2.4	689	5.6	3.7	4.2	4.8
Alcoholism and related liver disease							
No	5,475,640	97.9	11,950	96.8	1.8	2.3	2.5
Yes	117,876	2.1	398	3.2	2.5	3.5	3.0
Obesity							
No	5,543,143	99.1	12,158	98.5	1.8	2.3	2.5
Yes	50,373	0.9	190	1.5	3.6	4.5	3.7
Coronary heart disease							
No	5,358,377	95.8	9307	75.4	1.5	1.8	2.0
Yes	235,139	4.2	3041	24.6	13.9	17.3	14.6
Diabetes							
No	5,426,241	97.0	8343	67.6	1.3	1.6	1.7
Yes	167,275	3.0	4005	32.4	19.2	23.4	22.9
Hypertension							
No	5,431,660	97.1	9502	77.0	1.5	1.8	2.0
Yes	161,856	2.9	2846	23.0	15.5	22.1	29.0
Acute kidney failure							
No	5,586,700	99.9	11,850	96.0	1.7	2.2	2.4
Yes	6816	0.1	498	4.0	90.6	88.4	88.3

with low deprivation to 2.3 per 1000 in neighbourhoods with moderate deprivation and 2.5 per 1000 in neighbourhoods with high deprivation. Similar trends of slight increases in cumulative incidence rates of ESRD with increasing level of neighbourhood-level deprivation were observed across all individual-level sociodemographic categories and comorbidities. Men (2.3 per 1,000 in low deprived neighbourhood) and women (1.3 per 1,000 in low deprived neighbourhood) had different overall cumulative incidence rates of ESRD.

4.2. Neighbourhood deprivation and ESRD in men

Table 2 shows the different models for men. In the crude model, the odds ratio (OR) for ESRD for men living in high- versus low-deprivation neighbourhoods was 1.32 (95% confidence interval [CI] 1.22–1.43). Neighbourhood-level deprivation was significantly associated with ESRD after adjustment for age (model 2) and age plus individual-level sociodemographic variables (model 3), and in the full model (model 4) adjusted for age, individual-level sociodemographics, and comorbidities. The OR for ESRD was high for several comorbidities: 1.28 for chronic lower respiratory diseases, 2.31 for coronary heart disease, 4.83 for hypertension, 7.32 for diabetes, and 9.35 for acute kidney failure. Age was included as a continuous variable in models 2, 3, and 4. The OR for ESRD increased by 1.05 for every year of increasing age in models 2 and 3. After adjustment for comorbidities, the OR for age was 1.02. Increased ORs for ESRD were noted in the full model (model 4) for men with low educational level or low family incomes, and for men who were never married, widowed, or divorced. The OR was significantly decreased for men living in middle-sized towns or small towns/rural areas compared with those living in large cities. A slightly but significantly decreased OR was also observed for women who had moved within the previous 5 years. Immigrants from Finland had a lower OR for ESRD than native Swedes. No other differences were observed regarding country of birth.

4.3. Neighbourhood deprivation and ESRD in women

Table 3 shows the different models for women. In the crude neighbourhood-level model, the OR for ESRD for women living in high- versus low-deprivation neighbourhoods was 1.51 (95% CI 1.37–1.67). Neighbourhood-level deprivation remained significantly associated with ESRD after adjustment for age (model 2) and age plus the individual-level sociodemographic variables (model 3). In the full model, additionally adjusted for comorbidities, the OR was 1.18 (95% CI 1.06–1.31). Age was included as a continuous variable in models 2, 3, and 4. The OR increased by 1.04 for every year of increasing age in models 2 and 3. After inclusion of comorbidities, the OR for age was 1.02. Increased ORs for ESRD were noted in the full model (model 4) for women with low educational level or middle family income, and for women who were never married, widowed, or divorced. The OR was significantly decreased for women living in small towns/rural areas compared with those living in large cities. A slightly but significantly decreased OR was also observed for women who had moved within the previous 5 years. Finnish women had a lower OR for ESRD than native Swedish women. Otherwise there was no association with country of birth. All included comorbidities except for obesity were significantly associated with ESRD in women. Especially high ORs were noted for diabetes (8.78), acute kidney failure (7.98), and hypertension (4.44).

4.3.1. Subanalysis

Of all the 12,348 cases with ESRD, 950 (7.7%) patients had a first diagnosis of CKD-5 without dialysis or transplantation, 4542 (36.8%)

Table 2
Odds ratios (ORs) and 95% confidence intervals (CI) for end stage renal disease (ESRD) in men; Results from multi-level logistic regression models.

	Model 1			Model 2			Model 3			Model 4			
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	P-value
Neighborhood deprivation (ref. low)													
Moderate	1.27	1.20	1.35	1.28	1.20	1.36	1.19	1.12	1.26	1.16	1.09	1.24	<0.001
High	1.32	1.22	1.43	1.45	1.34	1.56	1.25	1.15	1.35	1.17	1.07	1.27	<0.001
Age (years)				1.05	1.05	1.05	1.05	1.05	1.06	1.02	1.02	1.03	<0.001
Education level (ref. > 12 years)													
≤ 9 years							1.29	1.20	1.38	1.15	1.08	1.23	<0.001
10–12 years							1.20	1.13	1.28	1.10	1.03	1.17	0.003
Marital status (ref. married/cohabiting)													
Never married, widowed, or divorced							1.24	1.18	1.30	1.16	1.11	1.22	<0.001
Family income (ref. high income)													
Low income							1.29	1.20	1.39	1.25	1.17	1.34	<0.001
Middle–low income							1.39	1.31	1.49	1.31	1.23	1.40	<0.001
Middle–high income							1.30	1.22	1.38	1.23	1.16	1.31	<0.001
Country of origin (ref. Sweden)													
Finland							0.82	0.72	0.94	0.74	0.65	0.85	<0.001
Western countries							0.84	0.67	1.05	0.84	0.67	1.05	0.134
Eastern European countries							1.14	0.98	1.32	1.04	0.89	1.20	0.617
Middle Eastern countries							1.09	0.94	1.27	0.95	0.82	1.11	0.549
Others							1.02	0.92	1.12	0.97	0.88	1.08	0.576
Urban/rural status (ref. large cities)													
Middle-sized towns							0.84	0.79	0.88	0.90	0.85	0.95	<0.001
Small towns/rural areas							0.84	0.79	0.90	0.83	0.77	0.89	<0.001
Mobility (ref. not moved)							0.99	0.94	1.05	0.94	0.89	0.99	0.024
Chronic lower respiratory disease (ref. no)										1.28	1.15	1.43	<0.001
Alcoholism and related liver disease (ref. no)										0.92	0.82	1.03	0.162
Coronary heart disease (ref. no)										2.31	2.18	2.44	<0.001
Hypertension (ref. no)										4.83	4.56	5.11	<0.001
Diabetes (ref. no)										7.32	6.95	7.70	<0.001
Obesity (ref. no)										0.80	0.65	0.99	0.046
Acute kidney failure (ref. no)										9.35	8.26	10.57	<0.001
Variance (S.E.)	*0.067 (0.014)*			*0.053 (0.014)*			*0.041 (0.014)*			*0.068 (0.014)*			

Model 1 (the neighbourhood model) includes neighbourhood-level deprivation. Model 2 includes neighbourhood-level deprivation and age (as a continuous variable). Model 3 includes neighbourhood-level deprivation and the following sociodemographic variables as covariates: age (as a continuous variable), marital status, family income, education level, country of origin, urban/rural status, and mobility. Model 4 (the full model): model 3 + comorbidities.

Table 3
Odds ratios (ORs) and 95% confidence intervals (CI) for end stage renal disease (ESRD) in women; Results from multi-level logistic regression models.

	Model 1			Model 2			Model 3			Model 4			
	OR	95%	CI	OR	95%	CI	OR	95%	CI	OR	95%	CI	P-value
Neighborhood deprivation (ref. low)													
Moderate	1.27	1.17	1.37	1.25	1.15	1.35	1.13	1.05	1.23	1.10	1.01	1.20	0.021
High	1.51	1.37	1.67	1.59	1.44	1.75	1.30	1.17	1.44	1.18	1.06	1.31	0.001
Age (years)				1.04	1.04	1.04	1.04	1.04	1.04	1.02	1.01	1.02	<0.001
Education level (ref. > 12 years)													
≤9 years							1.63	1.49	1.78	1.39	1.27	1.52	<0.001
10–12 years							1.35	1.24	1.46	1.25	1.15	1.35	<0.001
Marital status (ref. married/cohabiting)													
Never married, widowed, or divorced							1.15	1.08	1.22	1.08	1.01	1.15	0.016
Family income (ref. high income)													
Low income							1.24	1.12	1.36	1.07	0.97	1.18	0.194
Middle–low income							1.39	1.27	1.52	1.17	1.06	1.28	<0.001
Middle–high income							1.20	1.09	1.31	1.10	1.00	1.20	0.046
Country of origin (ref. Sweden)													
Finland							0.76	0.65	0.89	0.66	0.56	0.78	<0.001
Western countries							0.93	0.68	1.26	0.96	0.71	1.31	0.842
Eastern European countries							1.23	1.02	1.47	1.04	0.86	1.26	0.689
Middle Eastern countries							1.06	0.86	1.31	0.88	0.71	1.08	0.230
Others							1.07	0.94	1.21	1.05	0.93	1.19	0.424
Urban/rural status (ref. large cities)													
Middle-sized towns							0.90	0.84	0.97	0.96	0.90	1.03	0.317
Small towns/rural areas							0.87	0.79	0.95	0.86	0.78	0.94	<0.001
Mobility (ref. not moved)							0.96	0.90	1.03	0.91	0.85	0.98	0.009
Chronic lower respiratory disease (ref. no)										1.41	1.25	1.60	<0.001
Alcoholism and related liver disease (ref. no)										1.31	1.06	1.62	0.012
Coronary heart disease (ref. no)										2.66	2.44	2.89	<0.001
Hypertension (ref. no)										4.44	4.11	4.80	<0.001
Diabetes (ref. no)										8.78	8.16	9.44	<0.001
Obesity (ref. no)										0.91	0.74	1.12	0.368
Acute kidney failure (ref. no)										7.98	6.59	9.67	<0.001
Variance (S.E.)	*0.070 (0.023)*			*0.059 (0.023)*			*0.047 (0.022)*			*0.073 (0.023)*			

Model 1 (the neighbourhood model) includes neighbourhood-level deprivation. Model 2 includes neighbourhood-level deprivation and age (as a continuous variable). Model 3 includes neighbourhood-level deprivation and the following sociodemographic variables as covariates: age (as a continuous variable), marital status, family income, education level, country of origin, urban/rural status, and mobility. Model 4 (the full model): model 3 + comorbidities.

patients were transplanted, and 6856 (55.5%) patients were in dialysis (Supplement Table 1). Sensitivity analysis was also performed for these three groups of ESRD patients. Among men the OR was similar for all three groups Supplement Table 2). The OR in the fully adjusted model was for ESRD patients without dialysis and transplantation 1.16 (95% CI 0.88–1.53), for transplanted ESRD patients 1.21 (95% CI 1.07–1.35), and for ESRD patients in dialysis 1.16 (95% CI 1.03–1.30) (Supplement Table 5). Among women the highest OR was observed for ESRD patients without dialysis and transplantation 1.61 (95% CI 1.12–2.31) (Supplement Table 3). The OR in the fully adjusted model was for transplanted ESRD patients 1.15 (95% CI 1.00–1.34), and the OR for ESRD patients in dialysis was 1.22 (95% CI 1.05–1.43) (Supplement Table 3).

4.4. Sensitivity analysis

ESRD is a heterogeneous group regarding to aetiology. We have therefore also done analysis with exclusion of patients with the following diagnoses: cystic kidney disease (ICD-10 Q61), congenital kidney and urinary tract malformations (Q60, Q62, Q63, Q64), urolithiasis (N20-N23), rare inherited kidney diseases such as Alport's syndrome and Laurence–Moon–Biedl–Bardet syndrome (Q87.8A, Q87.8B), hyperoxaluria (E74.8B), glomerular disease (N00-N08), and tubular interstitial diseases (N10-N16). Totally 3,1% (n = 172055) of the total study population (5593516) was excluded. Among ESRD cases, these diagnoses constituted 46% (n = 5691) of all 12348 ESRD patients. The association between neighbourhood deprivation and ESRD became even stronger for both women and men after the exclusions (Supplement Tables 4 and 5). In the fully adjusted model 4, the OR in highly deprived neighbourhoods was 1.33 (95% CI 1.1.19–1.49) for men and 1.31 (95% CI 1.13–1.51) for women.

5. Discussion

5.1. Principal findings

In this nationwide cohort study, we found an association between neighbourhood deprivation and ESRD, independently of individual-level sociodemographic factors and comorbidities in both men and women. This association remained significant in the full model, which took account of individual-level sociodemographic factors, including SES, and comorbidities. Previous studies have found divergent results regarding the importance of individual-level SES and neighbourhood-level SES in CKD [13,17–19]. The present study is a nationwide study with high coverage and very high statistical power. It confirms that the incidence of ESRD is greater in patients of lower SES [4–19] and that both individual- and neighbourhood-level SES are important regarding the odds of developing ESRD, even after adjustment for comorbidities. However, the OR for ESRD was lower after adjustment for comorbidities, suggesting that the effect of low individual- and neighbourhood-level SES is partially mediated through these conditions.

In the present study only immigrants from Finland had a lower risk of ESRD than individuals born in Sweden (Tables 2 and 3). As this association remained after adjustments in the full model, a genetic cause is possible. No other significant differences were observed regarding country of birth. The present study adds to previous studies indicating that ethnicity may affect the risk of CKD and ESRD [31]. For example, in the USA the risk of ESRD was reportedly increased in blacks, Hispanics, and Asians compared to whites [31]. A higher risk for ESRD in

blacks compared with other races was also reported in the USRDS Annual Data Report [32].

Individual- and neighbourhood-level SES have been reported to be associated with CKD and ESRD [4–19]. However, the causal pathways between neighbourhood-level SES and poor health outcomes are not fully understood, and several possible mechanisms could lie behind our findings. One possible mediator could be psychological stress [33,34] due to littered and unsafe environments, vandalism, isolation/alienation, and violent crime [35] in deprived neighbourhoods. Additionally, socio-cultural norms regarding diet, smoking, and physical activity could vary between neighbourhoods and affect the health of residents and the risk of disease [36]. For instance, a Swedish study showed that CVD risk factors including physical inactivity, obesity, and smoking were more common among individuals living in deprived neighbourhoods than among those living in affluent neighbourhoods [37].

In Sweden, medical care is provided to all permanent residents, and primary health care clinics and hospitals are equally distributed and located in all types of neighbourhoods [38]. However, the actual number of health care professionals working in primary health care clinics can vary depending on the neighbourhood. This is related to difficulties in recruiting and retaining health care staff in high-deprivation neighbourhoods [39]. The uneven distribution of medical staff across neighbourhoods has also been documented in the UK [40], another country with universal health care.

5.2. Study limitations and strengths

Our study has some limitations. The study is an observational study and causality cannot be established. In studies of neighbourhood effects on health, selective residential mobility—the tendency of individuals to move to neighbourhoods whose characteristics match their individual characteristics (for example, the tendency of individuals with low SES to move to low-SES neighbourhoods)—can cause compositional neighbourhood differences. However, we adjusted for individual-level SES, which may improve our ability to differentiate between compositional and contextual effects on ESRD. There was a low correlation between the individual-level socioeconomic factors and neighbourhood deprivation (<0.2) and both individual-level and neighbourhood-level socioeconomic factors appear to be of importance. Although we adjusted also for mobility we cannot completely disentangle compositional from contextual effects on ESRD. Moreover, we have no data about smoking and body mass index in the study population. Though we adjusted for diagnoses of chronic lower respiratory diseases and obesity, residual bias is likely to exist.

Unfortunately, we have no information on race or ethnicity. However, we have information about country of birth. In models 3 and 4, the results were adjusted for country of birth. Sweden is a country with a highly heterogeneous population; 26% are first- or second-generation immigrants, which makes the results generalizable to other countries. Variations in MYH9 and APOL1 are associated with non-diabetic chronic kidney disease in individuals of African origin [1]. However, only 46,213 persons (0.8%) were born in Africa. In addition, of the 12348 ESRD cases only 0.9% (n = 109) cases were born in Africa. Thus, the MYH9 and APOL1 gene variants that are more common in individuals of African descent should not have affected the results to any major degree [1].

Our study also has a number of strengths. The large cohort included practically all patients aged 20–69 years with ESRD diagnoses in the Swedish Hospital Discharge Register and Outpatient Register during the study period, which increases the generalisability of our results. Another strength is the use of personal identification numbers, which made it possible to follow individuals in different registers [41]. Data in the Swedish Hospital Discharge Register are almost complete. In 2001, identification numbers were 99.6% complete and the main diagnosis was missing for only 0.9% of hospitalisations [42]. A further strength is the high validity of the Hospital Discharge Register [21,22,43]. About 85–95% of most diagnoses have been shown to be correct [21,22,43]. A limitation is that there has been no specific validation study for ESRD. However, validity for surgery procedure codes is generally high [21]. This is exemplified by the fact that for kidney transplantation there is 95% agreement between the Swedish Hospital Discharge Register and the Swedish Renal Registry [44]. The Swedish Renal Registry is a voluntary quality registry for patients with chronic renal failure in Sweden, and is maintained by the Swedish Renal Medical Association and the Swedish Transplantation Society. However, for the diagnosis of ESRD in patients without dialysis or transplantation the agreement is lower. For the diagnosis codes N18.4 (stage 4 CKD) and N18.5 (stage 5 CKD), agreement with the Swedish Renal Registry is only 36%, with coverage of 61% [45]. This is probably due to the use of N18.9 (unspecified renal failure) instead of N18.4 and N18.5 [45]. However, with regard to neighbourhood deprivation, this possible underreporting of N18.4 and N18.5 in the Swedish Hospital Discharge Register is most likely a source of non-differential bias. Moreover, in the present study only the N18.5 code (stage 5 CKD) was used; N18.4 (stage 4 CKD) was not used. The code N18.5 accounted for only 7.7% of patients (Supplementary Table 1). Thus, the present study mainly reflects patients with stage 5 CKD, who are treated with dialysis or renal transplantation.

5.3. Implications

The clustering of ESRD in deprived neighbourhoods raises clinical and public health concerns. The present findings suggest a need for a stronger focus on primary and secondary prevention of ESRD in deprived neighbourhoods.

6. Conclusion

Neighbourhood deprivation is associated with ESRD, independently of individual-level sociodemographic factors and comorbidities. These findings raise important clinical and public health concerns and indicate that both individual- and neighbourhood-level SES are important to consider in health care policies for patients with ESRD.

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Conflict of interests

No conflict of interest exists and all authors had full access to all the data used in the study and take full responsibility for the decision to submit the manuscript for publication.

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Paper II

PLOS ONE

RESEARCH ARTICLE

Familial Risks of Kidney Failure in Sweden: A Nationwide Family Study

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Abstract

Background: The value of family history as a risk factor for kidney failure has not been determined in a nationwide setting.

Aim: This nationwide family study aimed to determine familial risks for kidney failure in Sweden.

Methods: The Swedish multi-generation register on 0–78-year-old subjects were linked to the Swedish patient register and the Cause of death register for 1987–2010. Individuals diagnosed with acute kidney failure (n=10063), chronic kidney failure (n=18668), or unspecified kidney failure (n=3731) were included. Kidney failure patients with cystic kidney disease, congenital kidney and urinary tract malformations, urolithiasis, and rare inherited kidney syndromes, and hyperoxaluria were excluded. Standardized incidence ratios (SIRs) were calculated for individuals whose parents/siblings were diagnosed with kidney failure compared to those whose parents or siblings were not.

Results: The concordant (same disease) familial risks (sibling/parent history) were increased for chronic kidney failure SIR=2.02 (95% confidence interval, CI 1.90–2.14) but not for acute kidney failure SIR=1.08 (95% CI 0.94–1.22) and for unspecified kidney failure SIR=1.25 (95% CI 0.94–1.63). However, the discordant (different disease) familial risk for acute kidney failure SIR=1.19 (95% CI 1.06–1.32) and unspecified kidney failure SIR=1.63 (95% CI 1.40–1.90) was significantly increased in individuals with a family history of chronic kidney failure. The familial risk for chronic kidney failure was similar for males SIR=2.04 (95% CI 1.90–2.20) and females SIR=1.97 (95% CI 1.78–2.17). Familial risks for chronic kidney failure were highest at age of 10–19 years SIR=6.33 (95% CI 4.16–9.22).

Conclusions: The present study shows that family history is an important risk factor for chronic kidney failure but to a lower degree for acute kidney failure and unspecified kidney failure.

Introduction

Chronic kidney disease (CKD) is a worldwide medical problem with poor outcomes, high costs, and increased risk of cardiovascular comorbidities and all-cause mortality [1–3]. In developed countries, it is associated with old age, diabetes, hypertension, obesity, and cardiovascular disease [1]. Diabetic glomerulosclerosis and hypertensive nephrosclerosis are the presumed pathological entities but exact diagnosis is often difficult [1]. Familial and genetic factors are increasingly recognized as important for the development of CKD and end-stage renal disease (ESRD) [4–8]. Ferguson et al. first reported that family history of ESRD is common among African Americans with ESRD [9]. Several case-series and case-control studies have confirmed the importance of family history of kidney disease in different populations of patients with CKD and/or ERSD [10–18]. However, few follow-up studies have determined the importance of family history of CKD and/or ESRD [19]. In one such study, Hsu et al. found a modest effect of self-reported family history of kidney disease (hazard ratio (HR)=1.40) [19]. No study has determined whether familial factors influence the risk of acute kidney failure, which is an increasing global problem [20].

Though multiple genetic loci have been associated with progressive kidney failure and function, [21–23] heritability estimates suggests that only a small proportion of the total heritable contribution to the phenotypic variation of CKD have been identified. Large-scale follow-up studies to determine the importance of family history of CKD may therefore be of clinical value for risk assessment, and may help for planning of genetic studies. Clustering of a disease in families may be caused both by both genetic and non-genetic factors [24]. Increased familial risks may indicate shared environmental and lifestyle factors are of importance for disease development, and not only inherited biological factors [25]. However, without familial clustering a genetic cause is unlikely [24].

To our knowledge, there has not been any nationwide follow-up study whose aim was to determine familial risks of kidney failure among offspring/siblings. This nationwide follow-up study determined the familial risks of different forms of kidney failure – chronic kidney failure, acute kidney failure and unspecified kidney failure (i.e., not specified whether it is acute or chronic) – in the offspring/siblings of individuals with kidney failure. The present study underlines the importance of familial factors in kidney failure.

Materials and Methods

The dataset used in this study was constructed by linking several national Swedish registers provided by the Swedish government-owned statistics bureau Statistics Sweden and the National Board of Health and Welfare [26]. The Swedish multigenerational register contains information on family relationships for index persons born in Sweden in 1932 and later. Individuals born in 1932 or later and who were alive 1987 constituted the present study population. Linkages were made to National Census data in order to ascertain individual-level

socioeconomic status, to the Swedish cause of death register (1987–2010), to the Swedish outpatient care register (2001–2010), and to the Swedish hospital discharge register (1987–2010), the last of which records nationwide dates of hospitalization and hospital diagnoses since 1987. All linkages were performed using the individual national identification number that is assigned to each resident in Sweden for their lifetime. This number was replaced by a serial number in order to preserve anonymity. The serial numbers were used to check that each individual was entered only once (for his or her first main or secondary diagnosis of kidney failure). Over 8.1 million individuals and their biological parents (3.8 million families) were included in the database; the oldest (born in 1932) were 78 years at the end of follow-up period, which ran from 1987–2010.

Predictor and outcome variables

The predictor variable was family history (in a sibling or parent) of kidney failure (defined below) between 1987 and 2010. Separate risks were also determined for parental and sibling history of kidney failure. The outcome variable was first main or secondary event of kidney failure (acute kidney failure, chronic kidney failure, unspecified kidney failure) in the Swedish hospital discharge register, the Swedish outpatient care register, or the Swedish cause of death register. Acute kidney failure was defined by the following ICD codes: 584 (ICD-9) and N17 (ICD-10). Unspecified kidney failure was defined by the following ICD codes: 586 (ICD-9) and N19 (ICD-10). Chronic kidney failure was defined by the following ICD and surgical codes: 585,V45B, and V56 (ICD-9); N18, N26, T82.4, Y84.1, Z49, Z94.0, and Z99.2 (ICD-10); 6070, 6071, 6072, 6073, 6077, 6079, 9211, 9212, 9213, 9314, and 9200 (dialysis or kidney transplantation related surgical codes for 1987–1996); and V9211, V9212, V9200, V9531, V9532, V9507, KAS00, KAS10, KAS20, KAS40, KAS50, KAS60, KAS96, KAS97, and JAK10, TJA33, TJA35, TKA20 (dialysis or kidney transplantation related procedure and surgical codes for 1997–2010). Only main and secondary diagnoses were considered to ensure high validity. Kidney failure patients with cystic kidney disease (Q61, ICD-10; and 753B, ICD-9), congenital kidney and urinary tract malformations (Q60, Q62, Q63, Q64, ICD-10; and 753A, 753C, 753D, 753E, 753F, 753G, 753H, 753W, 753X, ICD-9), urolithiasis (N20-N23, ICD-10; and 592, ICD-9), rare inherited kidney diseases such as Alports syndrome and Laurence Moon-Biedl-Bardet syndrome (Q87.8A, Q87.8B, ICD-10), and hyperoxaluria (E74.8B, ICD-10; and 271W, ICD-9) were excluded.

Individual variables included in the analysis

The following variables were included in the analysis: 1) Sex: males or female; 2) Age: Age at diagnosis was categorized into 5-year groups; 3) Time period: The follow-up period was divided into 5-year intervals in order to adjust for changes in incidence rates over time; 4) Socioeconomic status: For both males and females, socioeconomic status was defined by occupation, which was divided into six groups: (1) farmers, (2) blue-collar workers, (3) white-collar workers, (4)

professionals, (5) self-employed workers, and (6) others (economically inactive individuals including unemployed individuals and homemakers); 5) Geographic region of residence: To allow adjustment for regional differences in incidence rates, geographic region of residence was divided into three groups: (1) large city, i.e., Stockholm, Gothenburg, or Malmo; (2) Southern Sweden (excluding the large cities, all of which lie in Southern Sweden); and (3) Northern Sweden; and 6) Comorbidity. Comorbidity was defined as a main or secondary diagnosis at follow-up between 1987 and 2010 with the following ICD-codes in the Swedish hospital discharge register or the Swedish outpatient care register: 1) chronic obstructive pulmonary disease (490–496 (ICD-9) and J40–J47 (ICD-10)); 2) obesity (278A and 278B (ICD-9) and E65 and E66 (ICD-10)); 3) alcoholism and alcohol-related liver disease (291, 303, 571A, 571B, 571C, and 571D (ICD-9) and F10 and K70 (ICD-10)); 4) diabetes mellitus (250 (ICD-9) and E10-E14 (ICD-10)); 5) hypertension (401–405 (ICD-9) and I10-I15 (ICD-10)); 6) coronary heart disease (410–414 (ICD-9) and I20-I25 (ICD-10)); 7) heart failure (428 (ICD-9) and I50 (ICD-10)); 8) hyperlipidaemia (272A, 272B, 272C, 272D, and 272E (ICD-9) and E78.0, E78.1, E78.2, E78.3, E78.4, and E78.5 (ICD-10)); and 9) stroke (430–438 (ICD-9) and I60-I69 (ICD-10)).

Statistical Analysis

For the analysis of familial risks of kidney failure, a previously described method was used [27]. The method is described in detail by Hemminki et al [28] and takes into account clustering within families, since it is based on complete ascertainment of sib ships in affected individuals. Person-years at risk (i.e., the number of persons at risk multiplied by the time at risk) were calculated from the start of the follow-up on 1 January 1987 until diagnosis for kidney failure, death, emigration, or the end of the follow-up (31 December 2010) [29]. Age-adjusted incidence rates were calculated for the whole follow-up period, divided into 5-year periods [29]. Standardized incidence ratios (SIRs) were used to measure the relative risk of kidney failure in individuals with one or more parents with a history of kidney failure compared with individuals with parents without a history of kidney failure. Similar calculations were performed separately for siblings.

The familial SIRs were calculated as the ratio of observed (O) and expected (E) numbers of kidney failure cases using the indirect standardization method:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j}^{J} n_j \lambda_j^*} = \frac{O}{E^*}$$

where $O = \sum o_j$ denotes the total observed number of cases in the study group; E^* (the expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; o_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by cross-classification of the following adjustment variables: age

(5-year groups), sex, socioeconomic status, time period (5-year groups), geographic region of residence, and comorbidities. 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution [29].

Data values are accurate to two decimals places. All analyses were performed using SAS version 9.2 (Institute, Cary, NC, USA).

Ethical Considerations

Statistics Sweden and the National Board of Health and Welfare maintain the nationwide registers used in the present study. This study was approved by the Ethics Committee at Lund University (approval number 409/2008 Lund with complementary approvals dated September 1, 2009, and January 22, 2010) and recommendations of the Declaration of Helsinki were complied with. The ethics committee waived informed consent as a requirement.

Results

We analyzed familial risks of kidney failure in the siblings/offspring (aged 0–78 years) of individuals with kidney failure between 1987 and 2010 in Sweden. The population and number of diagnosis for kidney failure are presented in Table 1. A total of 8054071 individuals were included in this cohort. A total of 32462 individuals were diagnosed with kidney failure, 64% (20688) were males and 36% (11774) females (Table 1). Of these patients, 31.0% (10063) were diagnosed with acute kidney failure, 57.5% (18668) with chronic kidney failure, and 11.5% (3731) with unspecified kidney failure. Comorbidities were more common in patients with kidney failure than in the general population (Table 1). The lowest incidence rates for kidney failure were observed for children (Figure 1). The incidence rate for kidney failure increased with age in both sexes (Figure 1). At older ages, the incidence rate for kidney failure was higher for males than females (Figure 1). The incidence rate was highest for chronic kidney failure, and lowest for unspecified kidney failure (Figure 2).

Familial risk of kidney failure

Familial risks of kidney failure according to disease subtypes are presented in Table 2. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. The incidence rates for familial and non-familial kidney failure are presented Figure 3. Concordant (same disease in proband and exposed relative) and discordant (different disease in proband and exposed relative) risks were determined. The familial risks were highest for chronic kidney failure: the concordant familial SIR for chronic kidney failure was 2.02. The concordant familial risk was not significantly increased for acute kidney failure (SIR=1.08) and for unspecified kidney failure (SIR=1.25) (Table 2). However, discordant risks show that family history (sibling/parent) of chronic kidney failure is a risk factor for both acute kidney failure (SIR=1.19) and

Table 1. Study population and number of kidney failure events in individuals aged 0 to 78 years (born 1932 and later and alive in 1987).

	Males				Females				All			
	Population		Kidney failure events		Population		Kidney failure events		Population		Kidney failure events	
	No	%	No	%	No	%	No	%	No	%	No	%
Age at diagnosis (years)												
0–9			286	1.4			263	2.2			549	1.7
10–19			424	2.0			419	3.6			843	2.6
20–29			998	4.8			706	6.0			1704	5.2
30–39			1695	8.2			1100	9.3			2795	8.6
40–49			2698	13.0			1585	13.5			4283	13.2
50–59			4712	22.8			2557	21.7			7269	22.4
60–69			6700	32.4			3477	29.5			10177	31.4
70–78			3175	15.3			1667	14.2			4842	14.9
Subtype of kidney failure												
Acute kidney failure			6385	30.9			3678	31.2			10063	31.0
Chronic kidney failure			11872	57.4			6796	57.7			18668	57.5
Unspecified kidney failure			2431	11.7			1300	11.1			3731	11.5
Socioeconomic status												
Farmer	69645	1.7	609	2.9	50935	1.3	263	2.2	120580	1.5	872	2.7
Self-employed	161705	3.9	1591	7.7	106967	2.7	476	4.0	268672	3.3	2067	6.4
Professional	359536	8.7	2435	11.8	251700	6.4	720	6.1	611236	7.6	3155	9.7
White collar worker	1192177	29.0	5898	28.5	1390397	35.3	4421	37.5	2582574	32.1	10319	31.8
Blue-collar worker	1848695	45.0	9952	48.1	1689070	42.8	5750	48.8	3537765	43.9	15702	48.4
Other	480443	11.7	203	1.0	452801	11.5	144	1.2	933244	11.6	347	1.1
Region of residence												
Northern Sweden	427832	10.4	2120	10.2	402535	10.2	1290	11.0	830367	10.3	3410	10.5
Large city	1632588	39.7	8828	42.7	1575746	40.0	4861	41.3	3208334	39.8	13689	42.2
Southern Sweden	2051781	49.9	9740	47.1	1963589	49.8	5623	47.8	4015370	49.9	15363	47.3
Chronic obstructive pulmonary disease												
No	3910183	95.1	18979	91.7	3763810	95.5	10467	88.9	7673993	95.3	29446	90.7
Yes	202018	4.9	1709	8.3	178060	4.5	1307	11.1	380078	4.7	3016	9.3
Obesity												
No	4080976	99.2	20058	97.0	3885685	98.6	11217	95.3	7966661	98.9	31275	96.3
Yes	31225	0.8	630	3.0	56185	1.4	557	4.7	87410	1.1	1187	3.7
Alcoholism and related liver disease												
No	3994406	97.1	18453	89.2	3883021	98.5	11184	95.0	7877427	97.8	29637	91.3
Yes	117795	2.9	2235	10.8	58849	1.5	590	5.0	176644	2.2	2825	8.7
Diabetes Mellitus												
No	3998103	97.2	13930	67.3	3868649	98.1	8345	70.9	7866752	97.7	22275	68.6
Yes	114098	2.8	6758	32.7	73221	1.9	3429	29.1	187319	2.3	10187	31.4
Hyptertension												
No	3928928	95.5	10841	52.4	3791314	96.2	6965	59.2	7720242	95.9	17806	54.9
Yes	183273	4.5	9847	47.6	150556	3.8	4809	40.8	333829	4.1	14656	45.1

Table 1. Cont.

	Males				Females				All			
	Population		Kidney failure events		Population		Kidney failure events		Population		Kidney failure events	
	No	%	No	%	No	%	No	%	No	%	No	%
Coronary heart disease												
No	3975828	96.7	15160	73.3	3879307	98.4	9561	81.2	7855135	97.5	24721	76.2
Yes	136373	3.3	5528	26.7	62563	1.6	2213	18.8	198936	2.5	7741	23.8
Stroke												
No	4038432	98.2	17537	84.8	3892316	98.7	10276	87.3	7930748	98.5	27813	85.7
Yes	73769	1.8	3151	15.2	49554	1.3	1498	12.7	123323	1.5	4649	14.3
Hyperlipidemia												
No	4067712	98.9	19437	94.0	3917158	99.4	11233	95.4	7984870	99.1	30670	94.5
Yes	44489	1.1	1251	6.0	24712	0.6	541	4.6	69201	0.9	1792	5.5
Heart failure												
No	4068915	98.9	16408	79.3	3920737	99.5	9833	83.5	7989652	99.2	26241	80.8
Yes	43286	1.1	4280	20.7	21133	0.5	1941	16.5	64419	0.8	6221	19.2
All	4112201	100.0	20688	100.0	3941870	100.0	11774	100.0	8054071	100.0	32462	100.0

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unspecific kidney failure (SIR=1.63) (Table 2). Moreover, discordant risks show that family history (sibling/parent) of acute kidney failure is a risk factor for both chronic kidney failure (SIR=1.10) and unspecific kidney failure (SIR=1.30) (Table 2). Family history of unspecified kidney failure (sibling/parent) was a risk factor for chronic kidney failure (SIR=1.31) (Table 2). Family history of all kidney failure was a risk factor for all types of kidney failure (Table 2). Familial risks of kidney failure were determined in both males and females. There were no major sex differences (Table 2).

In Table 3, familial concordant risks are presented according to the affected relative. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Sibling history of chronic kidney failure showed the highest familial risk, with a concordant SIR of 2.52. The familial concordant risk for individuals with a parental history of chronic kidney failure was 1.67. There were no major sex differences. The familial concordant risks for acute and unspecified kidney failure were not significant (Table 3).

The familial concordant risks (parent/sibling history) were stratified according to age at diagnosis (Table 4). The familial risks for chronic kidney failure were highly age dependent and were highest risks at younger ages (SIR=6.33 between the age of 10 and 19 years). Increased concordant familial risk of 1.81 was noted also for chronic kidney failure for those aged 60 years or more (Table 4). The familial concordant risks for chronic kidney failure were increased in all age groups except those younger than 10 years. For acute kidney failure, the familial concordant risks were only significantly increased only in two age groups (Table 4). The familial risk for acute kidney failure before age of 10 years was high (SIR=14.21). The age of these six children with familial acute kidney failure were

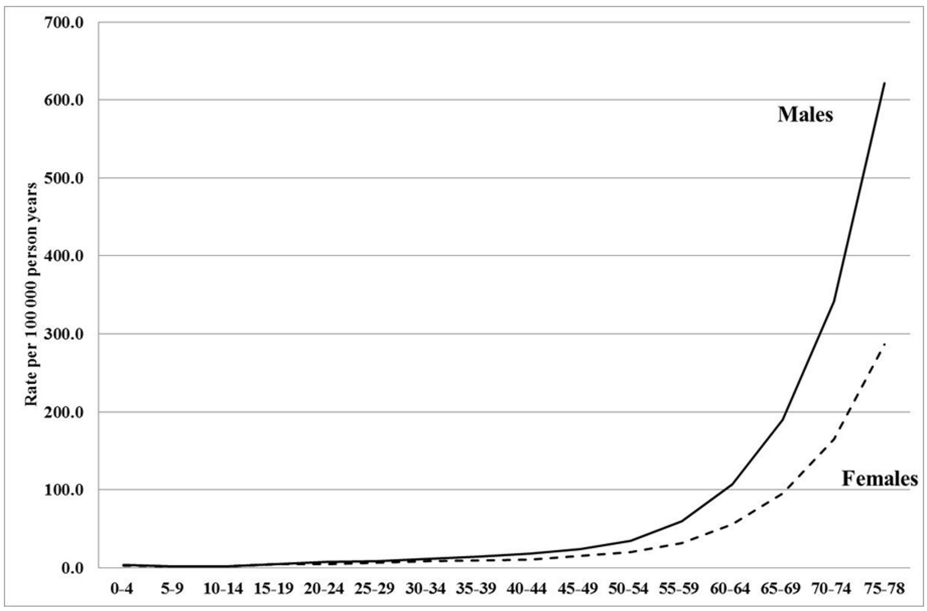

Figure 1. Age-specific incidence rates (per 100000 person years) of kidney failure for males and females in offspring/siblings born in 1932 and later.

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0, 1, 1, 5, 5, and 7 years. For three children, the diagnosis was unknown (two had ICD diagnosis=Z038 and one had no additional diagnosis). One child was prematurely born (<28 weeks) and/or had a very low birth weight (<1000 g) (ICD-9=765A), one had unspecified infectious gastroenteritis (ICD-9=009B), and one had gastroenteritis with Escherichia coli (ICD-9=008A). No significant increased risk for unspecified kidney failure was observed for any other age groups. However, the familial risk for all kidney failure was increased in all age groups (Table 4).

Test for the extent of the shared non-genetic familial contribution

In order to test for the extent of environmental sharing in the observed risks of kidney failure SIRs for siblings according to difference in age were calculated (Table S1). Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. Overall, the age difference

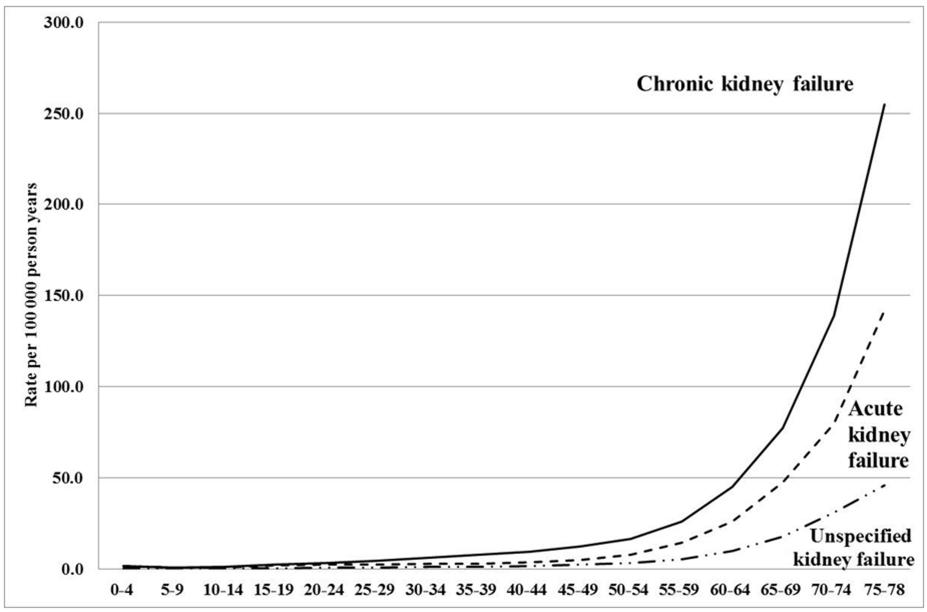

Figure 2. Age-specific incidence rates (per 100000 person years) of chronic kidney failure, acute kidney failure, and unspecified kidney failure (=others) in offspring/siblings born in 1932 and later.

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had little effect. Siblings with an age difference of <5 years showed a SIR for all kidney failure of 1.64 (95% CI, 1.50 to 1.79) compared with 1.72 (95% CI, 1.59 to 1.86) for those with an age difference of ⩾5 years. The concordant sibling risk for chronic kidney failure was 2.36 (95% CI 2.07–2.67) for siblings with an age difference of <5 years, compared with 2.65 (95% CI, 2.38 to 2.95) for those with an age difference of ⩾5 years.

Additional analyses

In Table S2, familial concordant and discordant risks are presented according to the affected relative. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. The results were basically similar to the familial concordant/discordant risk in Table 2. Thus, concordant and discordant risk was generally highest for chronic kidney failure, followed by unspecified kidney failure, and weakest for acute kidney failure independent of the type of affected relative (sibling/parent, parents, mother, father or sibling).

Table 2. Familial concordant and discordant risk (sibling/parent history) of kidney failure in males and females.

		Males				Females				All			
Type of kidney failure in proband	**Subtype of kidney failure in offspring/ sibling**	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Acute kidney failure	Acute kidney failure	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure	282	1.07	0.95	1.20	153	1.15	0.98	1.35	435	**1.10**	**1.00**	**1.21**
	Unspecified kidney failure	64	**1.29**	**1.00**	**1.65**	36	1.31	0.92	1.81	100	**1.30**	**1.06**	**1.58**
	All kidney failure	499	**1.10**	**1.01**	**1.20**	273	**1.14**	**1.01**	**1.28**	772	**1.11**	**1.04**	**1.19**
Chronic kidney failure	Acute kidney failure	201	1.15	0.99	1.32	129	1.26	1.05	1.50	330	**1.19**	**1.06**	**1.32**
	Chronic kidney failure	717	**2.04**	**1.90**	**2.20**	395	**1.97**	**1.78**	**2.17**	1112	**2.02**	**1.90**	**2.14**
	Unspecified kidney failure	104	**1.56**	**1.28**	**1.89**	65	**1.76**	**1.36**	**2.24**	169	**1.63**	**1.40**	**1.90**
	All kidney failure	1022	**1.72**	**1.62**	**1.83**	589	**1.73**	**1.59**	**1.88**	1611	**1.73**	**1.64**	**1.81**
Unspecified kidney failure	Acute kidney failure	72	1.07	0.84	1.35	42	1.04	0.75	1.41	114	1.06	0.88	1.28
	Chronic kidney failure	176	**1.31**	**1.12**	**1.52**	101	**1.31**	**1.07**	**1.60**	277	**1.31**	**1.16**	**1.47**
	Unspecified kidney failure	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
	All kidney failure	281	**1.22**	**1.09**	**1.38**	164	**1.24**	**1.06**	**1.44**	445	**1.23**	**1.12**	**1.35**
All kidney failure	Acute kidney failure	426	**1.11**	**1.01**	**1.22**	255	**1.15**	**1.01**	**1.30**	681	**1.12**	**1.04**	**1.21**
	Chronic kidney failure	1175	**1.57**	**1.48**	**1.66**	649	**1.58**	**1.46**	**1.71**	1824	**1.57**	**1.50**	**1.65**
	Unspecified kidney failure	201	**1.39**	**1.21**	**1.60**	122	**1.53**	**1.27**	**1.83**	323	**1.44**	**1.29**	**1.61**
	All kidney failure	1802	**1.41**	**1.35**	**1.48**	1026	**1.44**	**1.35**	**1.53**	2828	**1.42**	**1.37**	**1.48**

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00.
O=observed number of cases with family history of kidney failure; SIR=standardized incidence ratio; CI=confidence interval.

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Table S3 shows age stratified concordant and discordant familial risks (parent/siblings) of kidney failure. Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities. The results were basically similar to the familial age stratified concordant risks in Table 4. Thus, age stratified concordant and discordant risks were generally highest for chronic kidney failure, followed by unspecified kidney failure, and weakest for acute kidney failure independent of the type of affected relative (sibling/parent, parents, mother, father or sibling). However, for acute kidney failure, the familial concordant risks were highly increased in the two youngest age groups (Table S3).

Sensitivity analysis

Table S4 presents concordant and discordant familial risks (parent/siblings) after exclusion of patients with kidney cancer in parents/offspring. This did not change the results to any major degree.

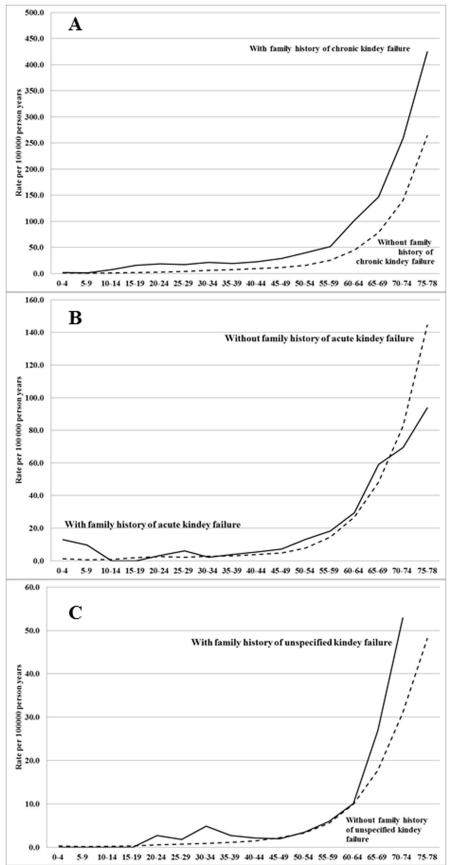

Figure 3. Age-specific incidence rate (per 100000 person years) of kidney failure by concordant family history of kidney failure in individuals born in 1932 and later. A Chronic kidney failure. B Acute kidney failure. C Unspecified kidney failure.

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Table S5 shows concordant and discordant familial risks (parent/siblings) for the follow up period 2001–2010. The familial risks were similar compared to using a follow-up period from 1987–2010. Thus, inclusion of outpatients with kidney

Table 3. Familial risk of concordant kidney failure in males and females.

		Males				Females				All			
Probands with any type of kidney failure	**Subtype of kidney failure in offspring/ siblings**	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Family history (parent/sibling)	Acute kidney failure	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
	Chronic kidney failure	717	**2.04**	**1.90**	**2.20**	395	**1.97**	**1.78**	**2.17**	1112	**2.02**	**1.90**	**2.14**
	Unspecified kidney failure	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
	All kidney failure	1802	**1.41**	**1.35**	**1.48**	1026	**1.44**	**1.35**	**1.53**	2828	**1.42**	**1.37**	**1.48**
Parents history	Acute kidney failure	103	1.06	0.87	1.29	58	1.10	0.83	1.42	161	1.07	0.91	1.25
	Chronic kidney failure	378	**1.71**	**1.54**	**1.89**	204	**1.62**	**1.40**	**1.85**	582	**1.67**	**1.54**	**1.82**
	Unspecified kidney failure	22	1.00	0.63	1.52	16	1.50	0.86	2.45	38	1.16	0.82	1.60
	All kidney failure	1124	**1.28**	**1.21**	**1.36**	637	**1.32**	**1.22**	**1.43**	1761	**1.29**	**1.23**	**1.35**
Paternal history	Acute kidney failure	62	1.20	0.92	1.54	26	1.03	0.67	1.51	88	1.14	0.92	1.41
	Chronic kidney failure	212	**1.73**	**1.50**	**1.98**	105	**1.45**	**1.19**	**1.76**	317	**1.62**	**1.45**	**1.81**
	Unspecified kidney failure	9	0.74	0.33	1.40	11	1.87	0.93	3.36	20	1.10	0.67	1.71
	All kidney failure	637	**1.35**	**1.24**	**1.45**	326	**1.21**	**1.08**	**1.35**	963	**1.29**	**1.21**	**1.38**
Maternal history	Acute kidney failure	42	0.92	0.66	1.25	33	1.19	0.82	1.67	75	1.02	0.80	1.28
	Chronic kidney failure	178	**1.69**	**1.45**	**1.96**	108	**1.88**	**1.54**	**2.27**	286	**1.76**	**1.56**	**1.97**
	Unspecified kidney failure	13	1.26	0.67	2.16	7	1.39	0.55	2.89	20	1.31	0.80	2.02
	All kidney failure	513	**1.20**	**1.10**	**1.31**	326	**1.47**	**1.31**	**1.63**	839	**1.29**	**1.21**	**1.38**
Sibling history	Acute kidney failure	52	1.15	0.86	1.50	27	0.98	0.64	1.43	79	1.08	0.86	1.35
	Chronic kidney failure	366	**2.52**	**2.27**	**2.80**	213	**2.52**	**2.19**	**2.88**	579	**2.52**	**2.32**	**2.73**
	Unspecified kidney failure	12	1.65	0.85	2.89	6	1.08	0.39	2.37	18	1.40	0.83	2.22
	All kidney failure	738	**1.68**	**1.56**	**1.80**	430	**1.70**	**1.54**	**1.87**	1168	**1.69**	**1.59**	**1.78**

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00.
O=observed number of cases with family history of kidney failure; SIR=standardized incidence ratio; CI=confidence interval.

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failure diagnosis from 2001 until 2010 did not change the results to any major degree.

Discussion

The present study is the first nationwide follow-up study to evaluate the familial risks of chronic, acute, and unspecified kidney failure among offspring/siblings of affected individuals. The results confirm previous case-series and case-control studies, which showed that familial factors are important for chronic kidney failure [9–18]. The present study adds follow-up data for a whole country. Previously a follow-up study only showed moderately increased familial risk

Table 4. Familial risk (sibling/parent history) of concordant kidney failure in males and females by age diagnosis.

	Males				Females				All			
Age at diagnosis (years)	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Acute kidney failure												
<10	4	**16.78**	**4.36**	**43.39**	2	**10.88**	**1.03**	**40.02**	6	**14.21**	**5.11**	**31.14**
10–19	0				0				0			
20–29	6	2.00	0.72	4.37	5	**3.70**	**1.17**	**8.70**	11	**2.52**	**1.25**	**4.53**
30–39	11	1.43	0.71	2.57	2	0.61	0.06	2.24	13	1.18	0.63	2.03
40–49	22	1.23	0.77	1.87	14	1.57	0.86	2.64	36	1.34	0.94	1.86
50–59	52	**1.35**	**1.01**	**1.78**	21	0.84	0.52	1.28	73	1.15	0.90	1.45
>=60	58	0.80	0.61	1.03	40	0.99	0.71	1.35	98	0.87	0.70	1.06
All	153	1.09	0.92	1.27	84	1.05	0.84	1.30	237	1.08	0.94	1.22
Chronic kidney failure												
<10	2	3.92	0.37	14.41	0				2	2.09	0.20	7.70
10–19	16	**6.94**	**3.96**	**11.30**	11	**5.60**	**2.78**	**10.06**	27	**6.33**	**4.16**	**9.22**
20–29	41	**4.87**	**3.49**	**6.61**	33	**4.35**	**2.99**	**6.12**	74	**4.62**	**3.63**	**5.81**
30–39	91	**2.36**	**1.90**	**2.90**	43	**1.76**	**1.27**	**2.37**	134	**2.13**	**1.78**	**2.52**
40–49	135	**2.08**	**1.75**	**2.47**	75	**2.11**	**1.66**	**2.65**	210	**2.09**	**1.82**	**2.40**
50–59	187	**1.86**	**1.60**	**2.14**	92	**1.74**	**1.40**	**2.14**	279	**1.82**	**1.61**	**2.04**
>=60	245	**1.81**	**1.59**	**2.05**	141	**1.81**	**1.52**	**2.14**	386	**1.81**	**1.63**	**2.00**
All	717	**2.04**	**1.90**	**2.20**	395	**1.97**	**1.78**	**2.17**	1112	**2.02**	**1.90**	**2.14**
Unspecified kidney failure												
<10	0				0				0			
10–19	0				0				0			
20–29	1	2.39	0.00	13.67	1	4.41	0.00	25.26	2	3.10	0.29	11.38
30–39	6	**2.80**	**1.01**	**6.12**	1	1.04	0.00	5.95	7	2.25	0.89	4.66
40–49	2	0.58	0.05	2.12	4	1.62	0.42	4.18	6	1.01	0.36	2.21
50–59	8	1.04	0.45	2.07	4	1.18	0.31	3.05	12	1.09	0.56	1.90
>=60	16	1.13	0.64	1.83	11	1.35	0.67	2.43	27	1.21	0.80	1.76
All	33	1.18	0.81	1.65	21	1.38	0.85	2.11	54	1.25	0.94	1.63
All kidney failure												
<10	6	**3.28**	**1.18**	**7.19**	6	**3.52**	**1.27**	**7.71**	12	**3.40**	**1.75**	**5.95**
10–19	23	**3.43**	**2.17**	**5.15**	24	**4.02**	**2.57**	**5.98**	47	**3.70**	**2.72**	**4.93**
20–29	72	**2.53**	**1.98**	**3.18**	56	**2.83**	**2.14**	**3.68**	128	**2.65**	**2.21**	**3.15**
30–39	180	**1.74**	**1.49**	**2.01**	87	**1.47**	**1.18**	**1.82**	267	**1.64**	**1.45**	**1.85**
40–49	290	**1.45**	**1.29**	**1.63**	178	**1.58**	**1.36**	**1.83**	468	**1.50**	**1.37**	**1.64**
50–59	515	**1.41**	**1.29**	**1.54**	260	**1.30**	**1.15**	**1.47**	775	**1.37**	**1.28**	**1.47**
>=60	716	**1.25**	**1.16**	**1.35**	415	**1.32**	**1.20**	**1.46**	1131	**1.28**	**1.20**	**1.35**
All	1802	**1.41**	**1.35**	**1.48**	1026	**1.44**	**1.35**	**1.53**	2828	**1.42**	**1.37**	**1.48**

Familial risks were adjusted for age, sex, time period, region of residence, socioeconomic status, and comorbidities.
Bold type: 95% CI does not include 1.00. O=observed number of cases with family history of kidney failure; SIR=standardized incidence ratio; CI=confidence interval.

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(HR=1.40) [19]. The present results indicate that familial factors are important for chronic kidney failure in both males and females of all ages (except <10 years), although the familial risks were highest at ages 10–19 years (Table 4). This is in contrast to the findings that most risk alleles from genome wide association studies add little to the prediction of CKD [21–23]. It is possible that there are a large number of risk alleles that have yet to be discovered that may account for this discrepancy. Unique familial (environmental or genetic) factors may predispose individuals to chronic kidney failure. Support for a genetic contribution to chronic kidney failure comes from the observation that age difference between siblings had little influence (Table S1). If environmental factors were strong, one would expect higher risks for siblings with smaller age differences. For chronic kidney failure, the familial concordant risks were high (Table 2). The familial concordant risks for acute and unspecified kidney failure were not significant (Table 2). However, increased discordant familial risks show that familial factors also are involved in acute and unspecified kidney failure (Table 2), though to a lower degree than for chronic kidney failure. Acute kidney failure is instead more related to precipitating factors such as sepsis, complex surgery, diagnostic procedures requiring intravenous contrast continue, and drug-induced kidney injury [20]. Unspecified kidney failure is probably a mixture of patients with chronic and acute kidney failure. No previous study has reported familial risks for acute and unspecified kidney failure.

Of interest is the high familial risk for acute renal failure among children younger than ten years (SIR=14.21) and also children and teenagers between 10 and 19 years of age (SIR=2.52) (Table 4). Among the children younger than 10 years, 2 were related to infection and one to preterm birth and or/low birth weight, which argue against a genetic cause for these cases of acute renal failure. Three cases were unknown and we cannot exclude that in rare cases familial factors are important among children and teenagers. A study from Norway of acute renal failure identified 315 cases of acute renal failure among children under the age of 16 years [30]. The estimated incidence rate was 3.3 cases per 100 000 children. This is in range of out overall kidney failure incidence rate among children (Table 1). Most cases (43%) in the Norwegian study were children under the age of five years [30]. The authors identified 53 aetiologies and classified these into 30 aetiological groups: 25% were prerenal failure (n=75), 74% were intrinsic/renal failure (n=234), and 2% were postrenal failure (n=5). Nephritic syndromes was the most common cause (44%) of acute kidney failure, followed by haemolytic-uraemic syndrome (HUS) (15%) [30].

The present design has potential advantages and disadvantages. Strengths of the study include complete nationwide coverage from 1987 in a country with high standards of diagnosis, with diagnoses often being made by specialists during extended examinations in clinics. The Swedish hospital discharge register contains no information about diagnostic procedures, which is a limitation. Moreover, the validity of ICD codes for kidney disease has not been reported. However, the Swedish hospital discharge register has been extensively validated and its overall diagnostic validity is close to 90% [31–32]. A limitation is the inclusion of

asymptomatic early stages of renal failure. The Swedish ICD-9 code 585 has no sub codes for different stages of ESRD. Thus, a number of patients with unidentified early stages of renal failure are not included in the study, which most likely is a non-differential bias with regards to familial risks. Another likely non-differential bias regarding familial risks is that cases in probands and relatives before 1987 are unknown. Moreover, the number of comorbidities is rather low (Table 1), possible due to that diagnosis made in primary health are not included. No nationwide primary health care register exists in Sweden.

Another important strength of our study is that it was based on nationwide registers and was thus free of selection and recall bias. The Swedish multi-generation register and the Swedish hospital discharge register are validated data sources that have been proven to be reliable in the study of many diseases [26], [31]. Data in our dataset are almost 100% complete [26].

In summary, the present study found indications of strong aggregation of chronic kidney failure, while familial factors are less important in acute and unspecified kidney failure. Familial non-genetic factors contribute among husbands but not wives. Identification of the unique familial factors in chronic kidney failure will advance our knowledge about the pathogenesis of kidney failure.

Supporting Information

Table S1. Familial risk of concordant kidney failure among siblings by age at difference in siblings.
doi:10.1371/journal.pone.0113353.s001 (DOCX)

Table S2. Familial risk of concordant and discordant kidney failure in men and women.
doi:10.1371/journal.pone.0113353.s002 (DOCX)

Table S3. Familial risk (sibling/parent history) of concordant and discordant kidney failure in males and females by age at diagnosis.
doi:10.1371/journal.pone.0113353.s003 (DOCX)

Table S4. Familial risk (sibling/offspring) of concordant and discordant kidney failure in males and females, after excluding kidney cancer in parents/offspring.
doi:10.1371/journal.pone.0113353.s004 (DOCX)

Table S5. Familial risk of concordant and discordant kidney failure in males and females, follow-up 2001–2010.
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Author Contributions

Conceived and designed the experiments: DSA BZ KS JS XL. Performed the experiments: DSA BZ XL. Analyzed the data: DSA BZ KS JS XL. Contributed reagents/materials/analysis tools: DSA BZ JS KS XL. Wrote the paper: DSA.

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ORIGINAL ARTICLE

Familial risks of glomerulonephritis – a nationwide family study in Sweden

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ABSTRACT

Objective: Familial risks of glomerulonephritis (acute, chronic and unspecified glomerulonephritis) have not been studied. This study aims to determine the familial risks of glomerulonephritis.

Methods: Individuals born from1932 onwards diagnosed with glomerulonephritis (acute [n = 7011], chronic [n = 10,242] and unspecified glomerulonephritis [n = 5762]) were included. The familial risk (Standardized incidence ratio = SIR) was calculated for individuals whose parents/full-siblings were diagnosed with glomerulonephritis compared to those whose parents/full-siblings were not. The procedure was repeated for spouses. Familial concordant risk (same disease in proband and exposed relative) and discordant risk (different disease in proband and exposed relative) of glomerulonephritis were determined.

Results: Familial concordant risks (parents/full-sibling history) were: SIR = 3.57 (95% confidence interval, 2.77–4.53) for acute glomerulonephritis, SIR = 3.84 (3.37–4.36) for chronic glomerulonephritis and SIR = 3.75 (2.85–4.83) for unspecified glomerulonephritis. High familial risks were observed if two or more relatives were affected; the SIR was 209.83 (150.51–284.87) in individuals with at least one affected parent as well as one full-sibling. The spouse risk was only moderately increased (SIR = 1.53, 1.33–1.75).

Conclusions: Family history of glomerulonephritis is a strong predictor for glomerulonephritis, and is a potentially useful tool in clinical risk assessment. Our data *emphasize* the contribution of familial factors to the glomerulonephritis burden in the community.

➤ KEY MESSAGES

- The familial risks (full-sibling/parent history) of glomerulonephritis (acute, chronic and unspecified glomerulonephritis) have not been determined previously.
- The familial risks of glomerulonephritis were increased among individuals with family history of acute, chronic or unspecified glomerulonephritis.
- The familial risks of glomerulonephritis were slightly increased among spouses indicating a modest non-genetic contribution.
- Very high familial risks were observed in multiplex families, i.e. with one or more affected first-degree relatives.

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Cohort study; familial risks; glomerulonephritis; standardized incidence ratio

Introduction

Kidney diseases are a global health challenge among all societies across the world with high impact on morbidity and mortality (1,2). With an increasing global population and a higher prevalence of kidney diseases, the need for a more effective prevention and cost-effective approach to tackle this condition is necessary (3). Glomerulonephritis is a common cause of end-stage kidney failure worldwide (4). The most common forms of glomerulonephritis in adults are IgA nephropathy, focal and segmental glomerulosclerosis, and vasculitis (4). In children the most common forms are minimal change disease, focal and segmental glomerulosclerosis, lupus nephritis- and IgA nephropathy (4).

Several single genes have been identified in patients with glomerular diseases, such as steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis (5). However, single-gene disorders are rare diseases. Our knowledge regarding common polygenic variants involvement in the familial risks of glomerulonephritis is uncertain, though common variants have been

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associated with other kidney disorders. These include as variants in the *UMOD, PRKAG2, APOL1* and *MYH9* genes (5–9). Several studies have recognized that glomerulonephritis may run in families (10–12). However, the familial risks of these diseases remain to be determined.

Knowledge of familial risks could be of clinical use in identifying individuals with an increased risk for glomerulonephritis. Such knowledge may help clinicians to select high-risk individuals for disease screening. The aim of the present study was to determine the importance of familial factors to the glomerulonephritis burden in the community. We hypothesized that glomerulonephritis in parents/full-siblings is associated with an increased risk of glomerulonephritis in offspring/full-siblings. In addition, we determined spouse risks in order to reflect the non-genetic adult familial risks.

Material and methods

Study design

The dataset used in this study was constructed by linking several national Swedish registers provided by the Swedish Government-Owned Statistics Bureau, Statistics Sweden, and the National Board of Health and Welfare (13–17). The Swedish multigenerational register contains information on family relationships for index persons born in Sweden from 1932 onwards. Individuals aged 0–78 years constituted the present study population. Linkages were made to National Census data (in order to ascertain individual-level socioeconomic status), the Swedish cause of death register (1964–2010), the Swedish outpatient care register (2001–2010), and the Swedish hospital discharge register (1964–2010); the last of which records complete nationwide data of hospitalizations and hospital diagnoses since 1987. All linkages were performed using the national personal identification number that is assigned to each resident in Sweden for their lifetime. This number was replaced by a serial number in order to preserve anonymity (18). The serial numbers were used to check that each individual was entered only once (for his or her first main or secondary diagnosis of glomerulonephritis). Approximately, 8 million individuals and their biological parents (3.8 million families) were included in the database; the oldest (born in 1932) were 78 years at the end of the follow-up period, which ran from 1964 to 2010.

Predictor and outcome variables

The predictor variable was family history (in a full-sibling and/or parent) of glomerulonephritis (defined below) between 1964 and 2010. Family history was only based on registry records (Multi-generation register), which eliminates recall bias from the proband. Separate risks were determined for parental and full-sibling history of glomerulonephritis. Full siblings were defined from the Multi-generation register by having the same mother and father, and the term sibling in this paper, refers to full-sibling. Thus, individuals without any full-sibling alive any time during the follow-up period between 1987 and 2010 were excluded in the analysis of familial sibling risks. Risk for spouses was also calculated. Spouses were defined as individuals older than 25 years with a common oldest child. Thus, only spouses with children were included in the spouse analysis. The outcome variable was first main or secondary diagnosis of glomerulonephritis (acute, chronic and unspecified glomerulonephritis) in the Swedish hospital discharge register or the Swedish outpatient care register. Acute glomerulonephritis was defined by the following ICD codes (international classification of diseases): 590 (ICD-7), 580 (ICD-8-9) and N00-N01 (ICD-10). Unspecified glomerulonephritis was defined by the following ICD codes: 593 (ICD-7), 583 (ICD-8-9) and N05 (ICD-10). Chronic glomerulonephritis was defined by the following ICD codes: 592 (ICD-7), 582(ICD-8-9) and N03 (ICD-10). Main (the main cause for hospitalization) and secondary diagnoses were considered.

Individual variables included in the analysis

The following variables were included in the analysis: (1) Gender: males or females; (2) Age: age at diagnosis was categorized into five-year groups; (3) Time period: the follow-up period was divided into five-year intervals in order to adjust for changes in hospitalization rates over time; (4) Socioeconomic status: socioeconomic status was defined by occupation for both males and females, which was divided into six groups: (1) farmers, (2) blue-collar workers, (3) white-collar workers, (4) professionals, (5) self-employed workers and (6) others (economically inactive individuals including unemployed persons and homemakers); (5) Geographic region of residence: to allow adjustment for regional differences in hospitalization rates, geographic region of residence was divided into three groups: (1) Southern Sweden; (2) large cities; and (3) Northern Sweden. Large cities were defined as municipalities with a population of $>$200,000 and comprised the three largest cities in Sweden: Stockholm, Gothenburg and Malmö.

Statistical analysis

A previously described method was used (19) for the analysis of familial risks of glomerulonephritis.

The method is described in detail by Hemminki et al. (20) and takes into account clustering within families, since it is based on complete ascertainment of sibships in affected individuals. Person-years at risk (i.e. the number of persons at risk multiplied by the time at risk) were calculated from the start of the follow-up on 1 January 1964 until diagnosis for glomerulonephritis, death, emigration, or the end of the follow-up (31 December 2010) (13). Age-adjusted incidence rates were calculated for the whole follow-up period, divided into five-year periods (21). Standardized incidence ratios (SIRs) were used to measure the relative risk of glomerulonephritis in individuals with one or more parents with a history of glomerulonephritis, compared with individuals with parents without a history of glomerulonephritis. Similar calculations were performed separately for full-siblings.

The familial SIRs were calculated as the ratio of observed (O) and expected (E) numbers of glomerulonephritis cases using the indirect standardization method:

$$\mathrm{SIR} = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*}$$

where, $O = \sum o_j$ denotes the total observed number of cases in the study group; E^* (the expected number of cases) is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-years of risk (n_j) for the study group; o_j represents the observed number of cases that the cohort subjects contribute to the jth stratum; and J represents the strata defined by cross-classification of the following adjustment variables: age (five-year groups), sex, socioeconomic status, time period (five-year groups), and geographic region of residence. 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution (21). Power calculation was not performed, as the study population was a nationwide cohort.

Familial SIRs for males were compared directly with those for females through calculation of SIR ratios according to the method described by Breslow and Day (21). The SIR ratios represent the relative risks for familial glomerulonephritis in males compared with females. SIR ratios have the same interpretation as the relative risk parameters estimated in case-control studies. They represent the ratios of age-specific rates for different exposure categories.

Data values are accurate to two decimals places. All analyses were performed using SAS version 9.3 (Institute, Cary, NC).

Ethical considerations

Statistics Sweden and the National Board of Health and Welfare maintain the nationwide registers used in the present study. This study was approved by the Ethics Committee at Lund University (approval number 409/2008 Lund with complementary approvals dated 1 September 2009 and 22 January 2010) and the recommendations of the Declaration of Helsinki were complied with. The ethics committee waived informed consent as a requirement.

Results

Study population

We analyzed the familial risks of glomerulonephritis (acute, chronic and unspecified glomerulonephritis) in the full-siblings/offspring (aged 0-78 years) of 8,187,887 individuals assessed in the registers for a clinical diagnosis of glomerulonephritis between 1964 and 2010 in Sweden. A total of 23,015 individuals were diagnosed with glomerulonephritis: 61% (14,009) males and 39% (9006) females (Table 1). Individuals with acute glomerulonephritis 30.5% (n = 7011), chronic glomerulonephritis 44.5% (n = 10,242) and unspecified glomerulonephritis 25% (n = 5762) were included. Many individuals with glomerulonephritis were diagnosed at a young age.

Familial risks of glomerulonephritis

Familial risks of glomerulonephritis according to disease subtypes are presented in Table 2. Increased risks were observed for paternal, maternal, paternal and full-sibling history of glomerulonephritis. The familial risks were highest for chronic glomerulonephritis in all lines; the SIR for chronic glomerulonephritis and parental history of any glomerulonephritis was 3.18 (95% CI 2.81–3.58). The familial SIR was 1.64 (95% CI 1.32–2.01) for acute glomerulonephritis and 2.54 (95% CI 2.11–3.05) for unspecified glomerulonephritis. Familial risks of glomerulonephritis were increased both in females and males (Table 2).

Individuals with an affected full-sibling with any type of glomerulonephritis had a higher risk of chronic glomerulonephritis (SIR = 3.73, 95% CI 3.26–4.26). The sibling risks were also increased for acute glomerulonephritis (SIR = 2.93, 95% CI 2.38–3.56) and unspecified glomerulonephritis (SIR = 3.37, 95% CI 2.75–4.10) (Table 2). The sibling risks were generally higher than the parent-offspring risks.

Familial risks of glomerulonephritis in different ages

In Table 3, familial risks are presented according to the relative affected (parents or full-siblings) at different ages. Familial risks were increased in all age groups. The parental risk was highest for individuals aged 30–39 years (SIR = 3.38, 95% CI 2.76–4.10). The sibling risk was highest for individuals aged 20–29 years (SIR = 4.74, 95% CI 3.85–5.78).

Table 1. Characterstics of Swedish patients with glomerulonephritis born 1932 until 2010.

	Males		Females		All	
	No.	%	No.	%	No.	%
Subtype of glomerulonephritis						
Acute	4357	31.1	2654	29.5	7011	30.5
Chronic	6446	46.0	3796	42.1	10242	44.5
Unspecified	3206	22.9	2556	28.4	5762	25.0
Age at diagnosis (yrs)						
<10	2297	16.4	1526	16.9	3823	16.6
10–19	2595	18.5	1629	18.1	4224	18.4
20–29	2459	17.6	1572	17.5	4031	17.5
30–39	2223	15.9	1455	16.2	3678	16.0
40–49	1740	12.4	1106	12.3	2846	12.4
50–59	1512	10.8	983	10.9	2495	10.8
60–69	986	7.0	601	6.7	1587	6.9
≥70	197	1.4	134	1.5	331	1.4
Periods (years)						
1964–1973	1231	8.8	758	8.4	1989	8.6
1974–1983	3398	24.3	1887	21.0	5285	23.0
1984–1993	2626	18.7	1612	17.9	4238	18.4
1994–2003	3459	24.7	2215	24.6	5674	24.7
2004–2010	3295	23.5	2534	28.1	5829	25.3
Socioeconomic status						
Farmers	251	1.8	114	1.3	365	1.6
Self-employed workers	703	5.0	306	3.4	1009	4.4
Professionals	1507	10.8	583	6.5	2090	9.1
White-collar workers	4231	30.2	3529	39.2	7760	33.7
Blue-collar workers	7010	50.0	4233	47.0	11243	48.9
Others	307	2.2	241	2.7	548	2.4
Region of residence						
Large cities	5671	40.5	3819	42.4	9490	41.2
Southern Sweden	5972	42.6	3788	42.1	9760	42.4
Northern Sweden	2366	16.9	1399	15.5	3765	16.4
All	14009	100.0	9006	100.0	23015	100.0

Gender differences

We calculated gender differences for glomerulonephritis by estimating family risk ratios and incidence rate ratios between males and females. The SIR ratio (male/female) was 1.15 (95% CI 0.95–1.35), $p = 0.1553$. The incidence rate ratio (male/female) was 1.52 (95% CI 1.47–1.56), $p < 0.001$ (calculations were based on an incidence rate of 10.9 per 1,00,000 person years for males and 7.2 per 1,00,000 person years for females. Age- and gender-specific incidence rates of glomerulonephritis are presented in Figures 1 and 2.

Discordant familial risks of glomerulonephritis

Concordant (same disease in proband and offspring) and discordant (different disease in proband and offspring) familial risks are presented in Table 4. There were increased familial risks for individuals with affected family members (family history) of all types of glomerulonephritis. The concordant familial SIR for acute glomerulonephritis among individuals with a family history of acute glomerulonephritis was 3.57 (95% CI 2.77–4.53). The corresponding SIRs were 3.84 (95% CI 3.37–4.36), for chronic glomerulonephritis and 3.75 (95% CI 2.85–4.83) for unspecified glomerulonephritis. The discordant familial risks were also increased. A family history of any glomerulonephritis increased the

Table 2. Familial risks of glomerulonephritis (acute, chronic and unspecified) according to relatedness.

		Males				Females				All			
Relatives with any type of glomerulonephritis	Subtype of glomerulonephritis in cases	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Parents history	Acute	60	**1.68**	**1.28**	**2.16**	34	**1.57**	**1.09**	**2.20**	94	**1.64**	**1.32**	**2.01**
	Chronic	156	**2.97**	**2.52**	**3.47**	109	**3.53**	**2.90**	**4.26**	265	**3.18**	**2.81**	**3.58**
	Unspecified	67	**2.58**	**2.00**	**3.28**	51	**2.49**	**1.86**	**3.28**	118	**2.54**	**2.11**	**3.05**
	All	283	**2.48**	**2.20**	**2.78**	194	**2.66**	**2.30**	**3.06**	477	**2.55**	**2.33**	**2.79**
Paternal history	Acute	38	**1.74**	**1.23**	**2.39**	19	1.44	0.86	2.25	57	**1.63**	**1.23**	**2.11**
	Chronic	93	**2.93**	**2.36**	**3.59**	62	**3.28**	**2.52**	**4.21**	155	**3.06**	**2.60**	**3.58**
	Unspecified	39	**2.47**	**1.76**	**3.38**	27	**2.17**	**1.43**	**3.17**	66	**2.34**	**1.81**	**2.98**
	All	170	**2.45**	**2.10**	**2.85**	108	**2.43**	**1.99**	**2.93**	278	**2.44**	**2.16**	**2.75**
Maternal history	Acute	24	**1.70**	**1.09**	**2.53**	16	**1.88**	**1.07**	**3.06**	40	**1.77**	**1.26**	**2.41**
	Chronic	63	**2.94**	**2.26**	**3.77**	47	**3.79**	**2.78**	**5.04**	110	**3.25**	**2.67**	**3.92**
	Unspecified	29	**2.79**	**1.87**	**4.01**	24	**2.92**	**1.87**	**4.35**	53	**2.85**	**2.13**	**3.72**
	All	116	**2.53**	**2.09**	**3.03**	87	**2.99**	**2.39**	**3.68**	203	**2.70**	**2.34**	**3.10**
Sibling history[a]	Acute	68	**3.11**	**2.42**	**3.95**	32	**2.60**	**1.78**	**3.67**	100	**2.93**	**2.38**	**3.56**
	Chronic	143	**3.72**	**3.14**	**4.39**	81	**3.75**	**2.98**	**4.66**	224	**3.73**	**3.26**	**4.26**
	Unspecified	68	**3.97**	**3.08**	**5.04**	33	**2.57**	**1.77**	**3.61**	101	**3.37**	**2.75**	**4.10**
	All	279	**3.61**	**3.20**	**4.06**	146	**3.12**	**2.64**	**3.67**	425	**3.42**	**3.11**	**3.77**
Spouse	Any types of glomerulonephritis	105	**1.54**	**1.26**	**1.86**	105	**1.52**	**1.24**	**1.84**	210	**1.53**	**1.33**	**1.75**

Bold type: 95% CI does not include 1.00.
O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.
Familial risks were adjusted for age, sex, time period, region of residence and socioeconomic status.
[a]Only individuals with at least one full-sibling were included in the analysis.

Table 3. Age- and sex-stratified familial risks of glomerulonephritis.

	Males				Females				All			
Age at diagnosis (years)	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Parental history												
<10	32	**1.68**	**1.15**	**2.38**	25	**2.04**	**1.32**	**3.02**	57	**1.83**	**1.38**	**2.37**
10–19	54	**2.44**	**1.83**	**3.18**	37	**2.71**	**1.91**	**3.74**	91	**2.54**	**2.05**	**3.12**
20–29	54	**2.60**	**1.96**	**3.40**	44	**3.37**	**2.45**	**4.53**	98	**2.90**	**2.36**	**3.54**
30–39	63	**3.42**	**2.63**	**4.37**	40	**3.31**	**2.37**	**4.52**	103	**3.38**	**2.76**	**4.10**
40–49	42	**2.96**	**2.13**	**4.01**	25	**2.71**	**1.75**	**4.01**	67	**2.86**	**2.22**	**3.64**
50–59	28	**2.38**	**1.58**	**3.44**	14	1.79	0.98	3.01	42	**2.14**	**1.54**	**2.90**
≥60	10	1.26	0.60	2.33	9	1.85	0.84	3.52	19	1.48	0.89	2.32
All	283	**2.48**	**2.20**	**2.78**	194	**2.66**	**2.30**	**3.06**	477	**2.55**	**2.33**	**2.79**
Full-sibling history[a]												
<10	28	**3.38**	**2.25**	**4.90**	9	1.79	0.81	3.42	37	**2.78**	**1.96**	**3.84**
10–19	65	**5.15**	**3.98**	**6.57**	26	**3.86**	**2.52**	**5.66**	91	**4.70**	**3.79**	**5.78**
20–29	61	**4.66**	**3.56**	**5.99**	38	**4.88**	**3.45**	**6.71**	99	**4.74**	**3.85**	**5.78**
30–39	50	**3.74**	**2.77**	**4.93**	20	**2.33**	**1.42**	**3.60**	70	**3.19**	**2.48**	**4.03**
40–49	26	**2.23**	**1.46**	**3.27**	26	**3.67**	**2.40**	**5.39**	52	**2.77**	**2.07**	**3.64**
50–59	25	**2.44**	**1.58**	**3.60**	19	**2.88**	**1.73**	**4.51**	44	**2.61**	**1.90**	**3.51**
≥60	24	**3.04**	**1.95**	**4.54**	8	1.62	0.69	3.20	32	**2.49**	**1.70**	**3.52**
All	279	**3.61**	**3.20**	**4.06**	146	**3.12**	**2.64**	**3.67**	425	**3.42**	**3.11**	**3.77**

Bold type: 95% CI does not include 1.00.
O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.
Familial risks were adjusted for age, sex, time period, region of residence and socioeconomic status.
[a]Only individuals with at least one sibling were included in the analysis.

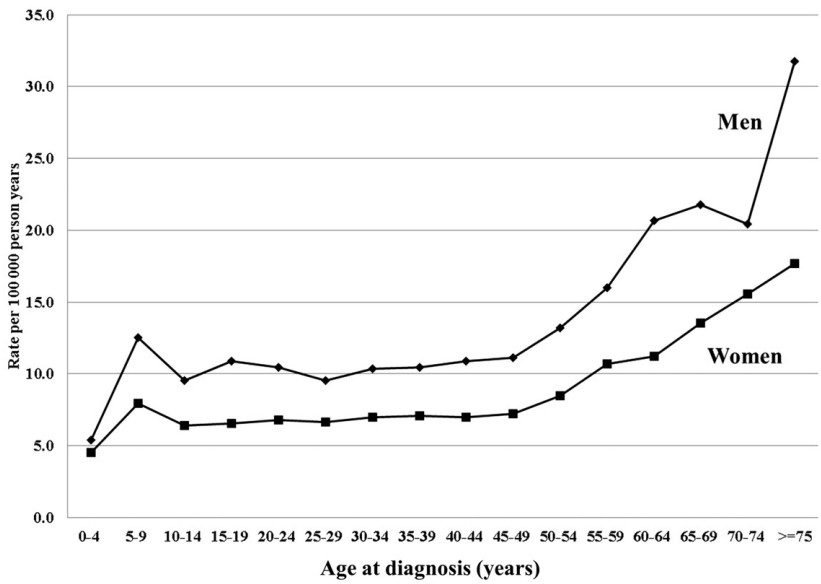

Figure 1. Age- and sex-specific incidence of glomerulonephritis in the Swedish population aged 0–78 years between 1964 and 2010.

risk of any glomerulonephritis disease; the SIR was 2.92 (95% CI 2.72–3.14).

Multiplex families

Familial SIRs for glomerulonephritis according to number and type of probands are summarized in Table 5. The SIR for glomerulonephritis in individuals with one affected parent was 2.54 (95% CI, 2.31–2.78). The SIR for glomerulonephritis when both parents were affected was 6.40 (95% CI, 1.67–16.55).

When at least one parent and one full-sibling were affected, the SIR was 209.83 (95% CI, 150.51–284.87).

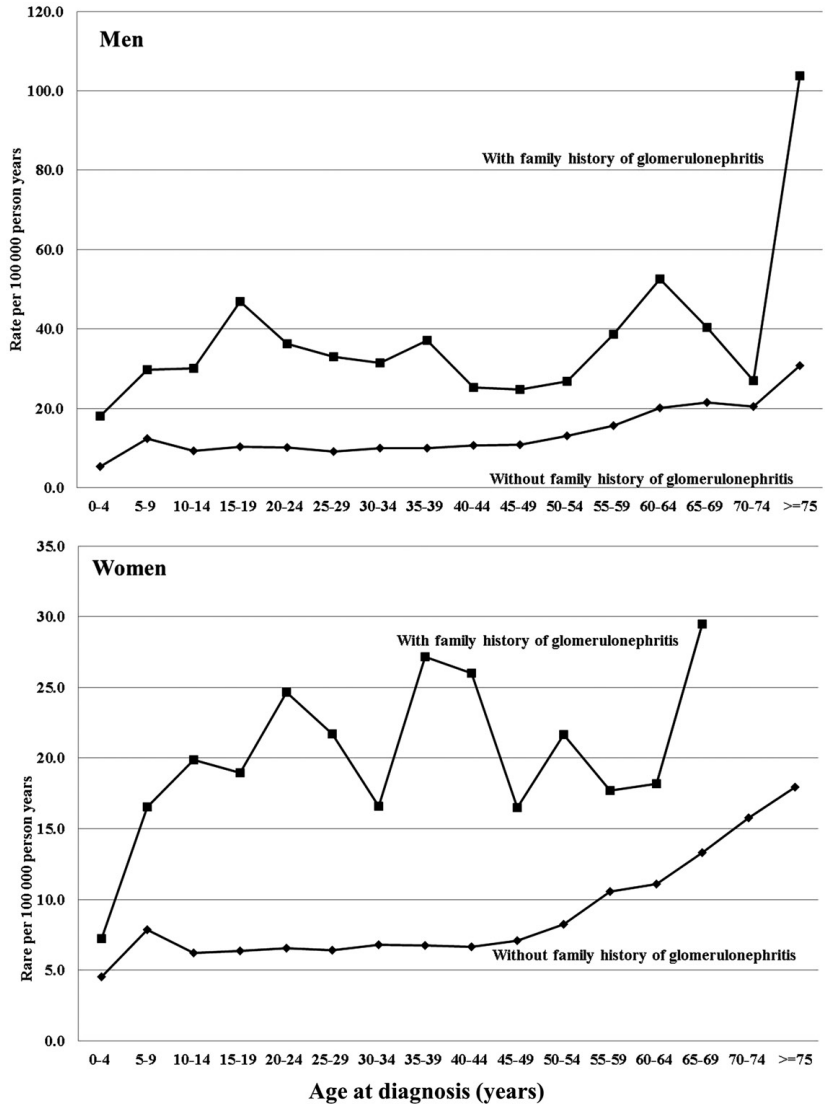

Figure 2. Age- and sex-specific incidence of glomerulonephritis in the Swedish population aged 0–78 years between 1964 and 2010 by presence or absence of family history (parent/full-sibling) of glomerulonephritis.

The SIR was 263.16 (95% CI, 173.25–383.35) when two full-siblings were affected. The familial SIR was 3.24 (95% CI, 2.93–3.58) for individuals with one affected full-sibling, and 263.16 (95% CI 173.25–383.35) for those with two affected full-siblings.

Test for the extent of the shared non-genetic familial contribution

Two kinds of analyses were performed to test for the extent of environmental sharing in the observed predictor of glomerulonephritis. Familial risks were

Table 4. Concordant and discordant familial risks (parent and/or full-sibling) of glomerulonephritis.

		Males				Females				All			
Disease in relative[a]	Subtype of glomerular diseases in cases	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Acute glomerulonephritis	Acute	50	**4.25**	**3.15**	**5.60**	17	**2.43**	**1.41**	**3.90**	67	**3.57**	**2.77**	**4.53**
	Chronic	31	**1.80**	**1.23**	**2.56**	19	**1.86**	**1.12**	**2.91**	50	**1.83**	**1.36**	**2.41**
	Unspecified	19	**2.28**	**1.37**	**3.56**	8	1.22	0.52	2.41	27	**1.81**	**1.19**	**2.64**
	All	100	**2.68**	**2.18**	**3.26**	44	**1.85**	**1.34**	**2.49**	144	**2.36**	**1.99**	**2.78**
Chronic glomerulonephritis	Acute	50	**2.10**	**1.56**	**2.77**	33	**2.39**	**1.65**	**3.36**	83	**2.21**	**1.76**	**2.74**
	Chronic	149	**3.76**	**3.18**	**4.41**	90	**3.97**	**3.19**	**4.88**	239	**3.84**	**3.37**	**4.36**
	Unspecified	64	**3.58**	**2.75**	**4.57**	40	**2.92**	**2.09**	**3.98**	104	**3.29**	**2.69**	**3.99**
	All	263	**3.23**	**2.85**	**3.65**	163	**3.25**	**2.77**	**3.79**	426	**3.24**	**2.94**	**3.56**
Unspecified glomerulonephritis	Acute	15	1.26	0.70	2.08	7	1.05	0.42	2.17	22	1.18	0.74	1.79
	Chronic	60	**3.12**	**2.38**	**4.02**	39	**3.69**	**2.63**	**5.05**	99	**3.32**	**2.70**	**4.05**
	Unspecified	37	**4.09**	**2.88**	**5.64**	22	**3.28**	**2.05**	**4.97**	59	**3.75**	**2.85**	**4.83**
	All	112	**2.78**	**2.29**	**3.35**	68	**2.84**	**2.21**	**3.60**	180	**2.81**	**2.41**	**3.25**
All	Acute	115	**2.42**	**2.00**	**2.90**	57	**2.08**	**1.57**	**2.69**	172	**2.29**	**1.96**	**2.66**
	Chronic	240	**3.16**	**2.77**	**3.58**	148	**3.41**	**2.88**	**4.01**	388	**3.25**	**2.93**	**3.59**
	Unspecified	120	**3.40**	**2.82**	**4.07**	70	**2.60**	**2.02**	**3.28**	190	**3.05**	**2.63**	**3.52**
	All	475	**2.99**	**2.73**	**3.27**	275	**2.81**	**2.49**	**3.16**	750	**2.92**	**2.72**	**3.14**

Bold type: 95% CI does not include 1.00.
O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status.
[a]Only individuals with at least one sibling were included in the analysis.

Table 5. Familial risk of glomerulonephritis according to number of affected relatives.

	Males				Females				All			
Affected relatives	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Parental history	283	**2.48**	**2.20**	**2.78**	194	**2.66**	**2.30**	**3.06**	477	**2.55**	**2.33**	**2.79**
One parent	280	**2.46**	**2.18**	**2.77**	193	**2.65**	**2.29**	**3.06**	473	**2.54**	**2.31**	**2.78**
Both parents	3	**7.51**	**1.42**	**22.22**	1	**4.44**	**0.00**	**25.47**	4	**6.40**	**1.67**	**16.55**
Parent and/or sibling history[a]	475	**2.99**	**2.73**	**3.27**	275	**2.81**	**2.49**	**3.16**	750	**2.92**	**2.72**	**3.14**
Parent without sibling history	196	**2.38**	**2.06**	**2.74**	129	**2.50**	**2.09**	**2.97**	325	**2.43**	**2.17**	**2.71**
Parent with one or more sibling	28	**216.22**	**143.54**	**312.86**	13	**197.27**	**104.61**	**338.30**	41	**209.83**	**150.51**	**284.87**
Sibling history[a]	279	**3.61**	**3.20**	**4.06**	146	**3.12**	**2.64**	**3.67**	425	**3.42**	**3.11**	**3.77**
One sibling	267	**3.49**	**3.08**	**3.93**	131	**2.84**	**2.37**	**3.37**	398	**3.24**	**2.93**	**3.58**
Two or more affected siblings	12	**237.62**	**122.19**	**416.38**	15	**287.91**	**160.64**	**476.02**	27	**263.16**	**173.25**	**383.35**

Bold type: 95% CI does not include 1.00.
O: observed cases; SIR: standardized incidence ratios; CI: confidence intervals.
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status.
[a]Only individuals with at least one sibling were included in the analysis.

calculated for spouses diagnosed with glomerulonephritis. The overall familial risk of any glomerulonephritis (acute, chronic and unspecified glomerulonephritis) was only modestly increased in spouses among males and females; the SIR was 1.53 (95% CI 1.33–1.75). Second, SIRs for full-sibling pairs (sib-pairs) according to age difference were calculated (Table 6). Siblings with a difference in age of less than five years had a SIR of 3.62 (95% CI 3.20–4.08) compared with 2.63 (95% CI 2.19–3.13) for those with a difference of at least five years (Table 6). Moreover, for chronic, unspecified and acute glomerulonephritis the familial risks tended to be highest among siblings with an age difference of less than five years, although the confidence intervals overlapped.

Discussion

Statement of new findings

The present study is the first nationwide follow-up study to evaluate the familial risks of glomerulonephritis (acute, chronic and unspecified glomerulonephritis) among offspring/full-siblings and spouses of affected individuals. Our results indicate that family history (parents and/or full-siblings) of glomerulonephritis is a strong predictor for glomerulonephritis. This is in agreement that causative mutations have been identified in patients with glomerular disease (6). The present results also indicate that other familial factors are important for glomerulonephritis in both males and females. Very high risks were noted among multiplex families, suggesting strong genetic factor segregation in these rare families (Table 5). Moreover, unique familial (environmental or genetic) factors may predispose individuals to glomerulonephritis. The familial concordant risks were high for chronic glomerulonephritis. The familial concordant risks for acute and unspecified glomerulonephritis were somewhat lower than those for chronic glomerulonephritis. The present study indicates that familial factors are of importance in acute, chronic and unspecified glomerulonephritis (Tables 2 and 4). The familial risk for

Table 6. Familial risk of glomerulonephritis in sib-pairs (full-siblings) by age difference.

		≤5 years				>5 years			
Sex	Subtype of glomerular diseases	O	SIR	95%	CI	O	SIR	95%	CI
Males	Acute	49	**3.76**	**2.78**	**4.97**	17	**1.97**	**1.14**	**3.15**
	Chronic	84	**3.61**	**2.88**	**4.47**	51	**3.41**	**2.54**	**4.49**
	Unspecified	46	**4.53**	**3.32**	**6.05**	20	**2.90**	**1.77**	**4.49**
	All	179	**3.85**	**3.31**	**4.46**	88	**2.89**	**2.32**	**3.56**
Females	Acute	20	**2.69**	**1.64**	**4.16**	11	**2.31**	**1.15**	**4.15**
	Chronic	51	**3.90**	**2.90**	**5.13**	20	**2.38**	**1.45**	**3.69**
	Unspecified	20	**2.61**	**1.59**	**4.03**	9	1.79	0.81	3.40
	All	91	**3.23**	**2.60**	**3.96**	40	**2.20**	**1.57**	**3.00**
All	Acute	69	**3.37**	**2.62**	**4.27**	28	**2.09**	**1.39**	**3.02**
	Chronic	135	**3.71**	**3.11**	**4.40**	71	**3.04**	**2.38**	**3.84**
	Unspecified	66	**3.70**	**2.86**	**4.71**	29	**2.43**	**1.63**	**3.49**
	All	270	**3.62**	**3.20**	**4.08**	128	**2.63**	**2.19**	**3.13**

Bold type: 95% CI does not include 1.00.
O: observed number of cases; SIR: standardized incidence ratio; CI: confidence interval.
Familial risks were adjusted for age, sex, time period, region of residence, and socioeconomic status.

unspecified glomerulonephritis was somewhere between that of the acute and chronic groups; the unspecified glomerulonephritis group may thus comprise a mixture of acute and chronic glomerulonephritis. Our study confirms previous studies that have recognized that glomerulonephritis run in families (10–12).

Testing genetic hypothesis

Spouses are genetically unrelated, but share adult environments and similar sociodemographic characteristics (22). Their family histories are thus matched in terms of many of the factors one might wish to control for in testing a genetic hypothesis. Spouse risks were low compared to familial risks in first-degree relatives. The spouse risk for glomerulonephritis was much lower than the sibling or offspring risks, suggesting that the familial risks in offspring and full-siblings to a large extent are genetic. The increased spouse risk may be related to shared familial environmental exposures, such as smoking, alcohol, diet, exercise habits and infections in adulthood (22). There was also a tendency for higher familial risks for glomerulonephritis in siblings with a difference in age of less than five years, which further suggests a non-genetic effect of shared familial environments. The exposure for environmental factors in different generations may vary. Such environmental factors could be infections, food and certain chemicals (23). However, the very high risk in multiplex families indicates a strong genetic cause (24). Another possible hypothesis for the tendency for higher sibling than parent-offspring risk could be due to recessive genes (6).

The Swedish hospital discharge register contains no information about diagnostic procedures (e.g. kidney biopsies), which is a limitation. Moreover, the use of ICD codes is limited given the distinction of acute, chronic and unspecified glomerulonephritis. This distinction largely has a historic basis and relates to a time when post-streptococcal glomerulonephritis was relatively common. Nowadays, many nephrologists have largely abandoned distinguishing between acute and chronic glomerulonephritis (4). This is reflected by the relative high rate of acute glomerulonephritis of 30.5% in the present study (4). We could not differentiate between primary and secondary glomerulonephritis. The lack of risk factors is a potential confounder, but it is probably a non-differential bias regarding familial risks. The validity of ICD codes for kidney disease has not been examined. However, the Swedish hospital discharge register has been extensively validated and its overall diagnostic validity is around 85-95% for most diseases (13,16). Moreover, specialist doctors in hospital care made the diagnosis. A good concordance of 89% was found between hospital discharge diagnoses and the underlying causes of death of those who were hospitalized and later died under dramatic conditions (25). As it is possible that the diagnostic accuracy could have varied between geographic regions, we adjusted for geographic region in order to minimize this possible bias. The higher risk associated with a family history might also, to a certain degree, be caused by detection bias/activity as well as a lower threshold for seeking medical help. However, the modest spouse risk suggests that this potential bias is modest regarding familial risks. The lack of nationwide data regarding family history before 1987 is also most likely a non-differential bias regarding family history of VTE. A most likely non-differential bias regarding familial risks is also that cases in probands and relatives before 1964 were unknown. Another limitation is that we had no data on life-style related factors, such as body mass index (BMI), smoking and diet, because it would be unrealistic to gather such data for an entire national population. However, we did adjust

for socioeconomic status, which is associated with many life-style factors, such as smoking. Another limitation is that some findings may have been caused by chance because of the multiple comparisons performed.

We calculated gender differences for glomerulonephritis by incidence rate ratios and family risk ratios between males and females. There were no differences in the familial risk between males and females (SIR ratio). However, glomerulonephritis was more common in males compared to females (incidence rate ratio).

Strengths of the study include complete nationwide coverage from 1987 in a country with high standards of diagnosis surveilled by the Swedish National Board of Health and Welfare, with diagnoses often being made by specialists during extended examinations in clinics. Thus, our data reflect the total impact of a familial history of glomerulonephritis in the whole population of Sweden. There is also an increasing number of Swedish National Quality Registers (around 100 registers) that contain individualized data concerning patient problems, medical interventions, and outcomes after treatment (26). Another important strength of our study is that it was based on nationwide registers and was thus free of recall bias. Selection bias was also minimized. The Swedish multigenerational register and the Swedish hospital discharge register are validated data sources that have been proven to be reliable in the study of many diseases (14–17). Data in our dataset are almost 100% complete (15).

Finally, although our study was limited to Sweden, the results from Swedish nationwide family studies are likely to be valid for Caucasian populations in Europe and the United States (17).

Conclusion

In summary, the present study found indications of strong familial aggregation in acute, chronic and unspecified glomerulonephritis. Familial adult non-genetic contributions are suggested to be moderate. Our data not only emphasize the contribution of familial factors to the glomerulonephritis burden in the community, but also suggest a causal relation of genetic factors to the disease process. Our findings suggest that information should be collected on parental/sibling glomerulonephritis as part of the family history to help identify persons at risk for glomerulonephritis.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Heritability of End-Stage Renal Disease: A Swedish Adoption Study

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Keywords
End-stage kidney disease · End-stage renal disease · Epidemiology · Genetic disease · Genetics

Abstract
Background/Aims: The heritability of end-stage renal disease (ESRD) among adoptees has not been examined so far. By studying adoptees and their biological and adoptive parents, it is possible to differentiate between the genetic causes and environmental causes of familial aggregation. This nationwide study aimed to disentangle the genetic and shared environmental contribution to the familial transmission of ESRD. ***Methods:*** We performed a family study for Swedish-born adoptees (born between 1945 until 1995) and their biological and adoptive parents. The Swedish Multi-Generation Register was linked to the National Patient Registry for the period 1964–2012. ESRD was defined as patients in active uremic care, that is, chronic dialysis or kidney transplantation. OR for ESRD was determined for adoptees with an affected biological parent with ESRD compared with adoptees without a biological parent with ESRD. The OR for ESRD was also calculated in adoptees with an adoptive parent with ESRD compared with adoptees with an adoptive parent without ESRD. Moreover, heritability for ESRD was estimated with Falconer's regression. ***Results:*** A total of 111 adoptees, 463 adoptive parents, and 397 biological parents were affected by ESRD. The OR for ESRD was 6.41 in adoptees (95% CI 2.96–13.89) of biological parents diagnosed with ESRD. The OR for ESRD was 2.40 in adoptees (95% CI 0.76–7.60) of adoptive parents diagnosed with ESRD. The heritability of ESRD was 59.5 ± 18.2%. ***Conclusion:*** The family history of ESRD in a biological parent is an important risk factor for ESRD. The high heritability indicates that genetic factors play an important role in understanding the etiology of ESRD.

Introduction

Familial and genetic factors are being increasingly recognized as important factors required for the development of end-stage renal disease (ESRD) and chronic kidney disease (CKD) [1–6]. Multiple studies have demonstrated the importance of family history of kidney disease among different populations of patients with ESRD [7–26]. Recent nationwide family studies have been performed concerning the association of renal failure and ESRD [27, 28]. A Swedish nationwide family study found an increased familial risk for chronic renal failure and unspecified renal failure but not for acute renal failure [27]. A significant familial risk for acute renal failure was observed only among young children [27]. In a recent nationwide Norwegian study, a strong familial risk of ESRD was found [28]. Though multiple genetic loci have been

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associated with progressive kidney failure and function [29–33], heritability estimates suggest that only a small proportion of the total heritable contribution to the phenotypic variation of CKD/ESRD have been identified. Clustering or aggregation of a disease in families may be caused both by genetic and non-genetic factors [34]. Increased familial risks may indicate that shared environmental and lifestyle factors and not only inherited biological factors are of importance for disease development and [34]. Twin studies are the most common way to determine the contribution of genetic and environmental factors, but according to Risch, adoption studies have a potential powerful design [34]. However, to the best of our knowledge, no such study has been conducted so far for ESRD in adoptees.

This study used the Swedish National Patient Register (NPR) and the Swedish Multi-Generation Register and aimed to examine the risk and heritability of ESRD in adoptees with a biological parent affected by ESRD. By heritability (h^2) we mean the genetic definition [34], that is, the degree of variation in a phenotypic trait (or disease) in a population that is due to variation in additive genetic factors.

Methods

Data were collected on adoptees and their biological and adoptive parents from 1964 to 2012 in order to disentangle the genetic and environmental influences associated with ESRD. We used several Swedish nationwide registers as part of our analyses [35–41]. Statistics Sweden and the National Board of Health and Welfare maintain the registers used in the present study. The Swedish personal identity number is issued to all residents in Sweden [40]. The Swedish personal identity numbers were used to link data from different registers. The coverage is practically complete [40]. These identity numbers were replaced by Statistics Sweden with serial numbers to secure anonymity. We used data from several sources:

1. The Swedish Multi-Generation Register, which encompass data on familial relationships including adoptions [37]. This register comprises data on index persons registered in Sweden after 1961 and born during and later than 1932.

2. The NPR, which contains all hospital diagnoses for all people in Sweden from 1964 to 2012. The register has had nationwide coverage since 1987. NPR also includes the Hospital Outpatient Register, which contains information on diagnoses from all hospital outpatient visits in Sweden between 2001 and 2012.

3. The Swedish Cause of Death Register, which encompass data on date and cause of death from 1964 to 2012.

4. The Total Population Register contains data on life events including birth, death, name change, marital status, family relationships, education and migration within Sweden as well as to and from other countries. Nearly 100% of births and deaths, 95% of immigrations and 91% of emigrations are reported to the Total Population Register [41].

5. From 1991, Small Area Market Statistics (SAMS) data are used to define a municipal subarea when you need to characterize a neighborhood; the code is comprised of the county, the municipality, and the unique SAMS area (9,200 in the whole of Sweden).

Definition of ESRD and Comorbidities

Patients with ESRD in the NPR (the Swedish Hospital Discharge Register [1964–2012] and Outpatient Register [2001–2012]) were identified by the International classification of diseases (ICD) codes and surgical and non-surgical interventions code for chronic dialysis and kidney transplantation, that is, patients in active uremic care (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000484327). Main and all secondary diagnoses were used. The validity in the Hospital Discharge Register is generally between 85 and 95% [38]. Diabetes mellitus, hypertension, and glomerulonephritis were identified by ICD codes any time during follow-up during the period 1964–2012 (online suppl. Table 2).

Sample

The analyses were based on a dataset that encompass all Swedish-born adoptees (born between 1945 and 1995) and their biological and adoptive parents. Adoptees were excluded from the study if they had died before age 16 (i.e., exclusion of possible severe congenital cases), migrated from Sweden before 16 years of age, died before 1964 (i.e., before start of follow-up), or if they were not linked to at least one biological and at least one adoptive parent. All adoptive children who had lived with a biological parent were excluded according to Census data (1960–1990) or SAMS data (from 1991). For those born between 1945 and 1960, the status in the 1960 census was used. Adoptees that had lived with their biological grandparent, aunt/uncle, and sibling or with step-parents together with their biological parent were also excluded. A total of 37,486 Swedish-born adoptees remained in the study after exclusions. They compose the study population in the cohort study. These adoptees could be linked to 64,139 adoptive parents and 59,287 biological parents.

After exclusions we identified 971 (0.59%) patients with ESRD among adoptees and their adoptive and biological parents. Of these 971 cases of ESRD, 111 were found in adoptees, 463 ESRD cases in biological parents, and 397 ESRD cases in adoptive parents. Of the 971 ESRD cases, 22.66% (n = 220) were found in the Hospital Outpatient register and 657 (67.66%) from the Hospital Discharge register through ICD codes (online suppl. Table 1). Moreover, the surgical codes (and non-surgical) version 6 (1963–1996) identified 4.74% (n = 46) ESRD patients, temporary non-surgical codes (1997–2006) identified 1.24% (n = 12) ESRD patients, and a new version of surgical codes (KVÅ, 1997–2012 and after 2007 also non-surgical codes) identified 3.71% (n = 36) ESRD patients. When factoring in, all ESRD cases 3.50% (n = 34) were identified with ICD-8 codes, 25.85% (n = 251) with ICD-9 codes, and 60.97% (n = 592) with ICD-10 codes.

Statistical Calculations

We used a cohort design but also a case-control approach in order to study genetic and non-genetic factors in ESRD among adoptees. We conducted 2 main analyses: ORs was determined with logistic regression in adoptees with an affected biological parent and in adoptees with an affected adoptive parent. We used case-control exact matching method (1:5) by drawing a sample of

ESRD affected adoptees as cases and matched control groups of ESRD unaffected adoptees [42]. The control group was matched based on gender, birth year, county of birth, and level of education. In the case-control study, we connected both groups to their biological and adoptive parents [43]. In the case-control study, OR was calculated with conditional logistic regression. In the cohort study, logistic regression was used to determine crude (univariate models for each variable; model 1 and 3) and multivariate (adjusted model; model 2 and 4) ORs for history of ESRD in biological (model 1 and 2) or adoptive parent (model 3 and 4). In the multivariate model (adjusted model 2 and 4), we used adoptees' birth year, gender, education of adoptees, and county of birth of adoptees as covariates in the cohort study. The estimated parameter was both in the case-control and case cohort study OR of ESRD in adoptees with at least one affected biological parent compared with adoptees without any affected biological parent, and similarly for adoptive parents. We performed a sensitivity analysis (using both the case-control and case cohort study design as described above) with both adoptive parents identified in order to determine the robustness of results and to test the effect of a lack of information about adoptive child status. Based on the assumption that if the prevalence of the disease is low (<10%), the OR approximates the relative risk; we used logistic regression to calculate ORs in both Case-Cohort and Case-Control studies. However, we also show the results of Cox regression to compare the results between logistic regression and Cox regression models. We also performed a Kaplan-Meier analysis. To fully take into account deaths, we also considered the competing risk of death. We determined the estimated cumulative incidence functions (CIF) for ESRD for adoptees stratified by biological parents with and without ESRD. In order to test hypotheses of equality of CIF between 2 adoptees with and without an affected parent we used Gray's test.

An important question in medicine is whether observed variation in a particular disease is due to environmental factors or biological factors (nature – nurture debate) [34, 44]. In genetics, heritability summarizes how heritable a disease of interest is, that is, the proportion of variance that emerges due to hereditary factors, especially with reference to the resemblance of offspring and parents. Formally heritability is defined as a ratio of variances, that is, the proportion of total variance that is due to variation in additive genetic factors (heritability = h^2) [34, 44]. According to classic quantitative genetics, the heritability (h^2) of a binary trait (or disease) could be estimated by Falconer's regression or from relatives' tetrachoric correlation by presuming a liability threshold model of the disease, where everyone has a liability to develop the disease, but only individuals above a threshold value do so [34, 45–47].

To evaluate heritability for ESRD, two different methods were used [45–47]. First we used Falconer's regression, which is based on the liability of the threshold, to obtain heritability in adoptees of the biological parents [46, 47]. The method and its application are described in detail by Falconer [47]. Using the prevalence rate of the relatives of the biological probands and the controls (i.e., biological parents to affected and unaffected adoptees respectively) from the case-control study, the heritability h^2 (and ± SE) was calculated [47]. We also used the approach described by Frisell et al. [45] using the tetrachoric correlation. This method allowed us to test the sensitivity of the calculated heritability to the assumed prevalence. The tetrachoric correlation is the inferred Pearson correlation from a 2 by 2 table with dichotomous normality being assumed. The tetrachoric correlation coefficient can vary from –1 (perfect negative correlation) through 0 (no correlation) to +1 (perfect positive correlation) in analogy with Pearson' correlation. Thus, using the case-control design we calculated tetrachoric correlation for a range of estimated population prevalence of ESRD [45]. Assuming that only additive genetic factors contribute to the similarity that exists among adoptees and their biological parent relatives, according to Falconer and Mackay, the heritability of liability was estimated to be twice the tetrachoric correlation among first-degree relatives (i.e., adoptees and their biological parents) [46].

Statistical analysis was performed with SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and we used R software (version 3.3.2) for calculating heritability.

Results

Descriptive Statistics

A total of 971 individuals were diagnosed with ESRD during the study period (1964–2012). This corresponds to a prevalence of 0.6% for ESRD during the whole study period. Table 1 shows the descriptive statistics for adopted offspring and their biological and adoptive parents, that is, gender, age at end of follow-up, birth year, educational attainments, cases with ESRD, the gender of ESRD cases, age at ESRD diagnosis, and age at end of follow-up for ESRD cases. The age distribution at the time of ESRD in adoptees is presented in Figure 1. The adoptive parents with a median age of 78 years (interquartile range [IQR] 69–85 years) were older than biological parents with a median age of 69 years (IQR 61–77 years) at the end of the follow-up period. Table 1 also shows that the median birth year of adoptees was 1961 (IQR 1953–1966), for biological parents it was 1937 (IQR 1928–1945), while it was 1925 (IQR 1917–1936) for adoptive parents. It was found that diabetes mellitus, hypertension, glomerulonephritis, and mortality were more common among study participants with ESRD compared to those without ESRD (Table 2).

Cohort Design

The calculated ORs with 95% CI in the cohort design are shown in Table 3. In the crude model (model 1), the OR for ESRD in adoptees of affected biological parents was increased; OR was 6.40 (95% CI 2.96–13.85). The OR in the adjusted model (model 2) was also significantly increased (OR 6.41; 95% CI 2.96–13.89). The calculated OR for ESRD in adoptees with an affected adoptive parent was not statistically significant in the crude model 3 (OR 2.23; 95% CI 0.71–7.05) or in the adjusted model 4 (OR 2.40; 95% CI 0.76–7.60).

Table 1. Descriptive statistics of the study population (n = 160,912) that constitutes Swedish-born adoptees between 1945 and 1995 and their adoptive and biological parents

	Adopted offspring (n = 37,486)	Adoptive parents (n = 64,139)	Biological parents (n = 59,287)
Gender, females, n (%)	18,220 (48.60)	29,219 (45.56)	35,743 (60.29)
Age at end of follow-up, years, median (Q1–Q3)	51 (45–59)	78 (69–85)	69 (61–77)
Birth year, mean (SD)	1961 (10)	1927 (13)	1936 (12)
Birth year, median (Q1–Q3)	1961 (1953–1966)	1925 (1917–1936)	1937 (1928–1945)
Birth year, range (maximum–minimum)	1945–1995	1883–1979	1877–1980
High education, >12 years, n (%)	10,731 (28.63)	9,552 (14.89)	5,283 (8.91)
ESRD cases, n (%)	111 (0.30)	463 (0.72)	397 (0.67)*
Gender of ESRD cases, females, n (%)	47 (0.13)	175 (0.27)	214 (0.36)
Age at ESRD diagnosis, years, median (Q1–Q3)	45 (37–56)	71 (60–77)	66 (57–73)

Q1–Q3, first quartile–third quartile; ESRD, end-stage renal disease.
* One adopted offspring had 2 biological parents with ESRD.

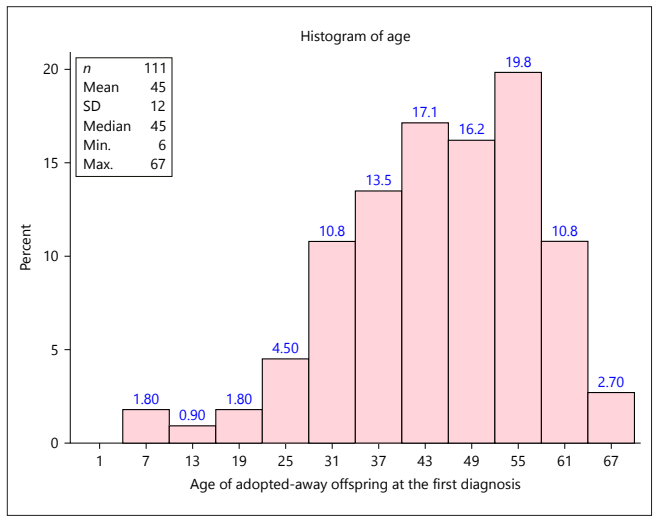

Fig. 1. Age distribution for Swedish-born (1945–1995) adoptees when ESRD was diagnosed first. ESRD, end-stage renal disease.

The Kaplan-Meier analysis in Figure 2 compares the ESRD-free survival between adoptees with affected (ESRD) biological parents with unaffected biological parents. The log-rank test (p value <0.0001) indicates that differences between the groups are statistically significant. Using Cox regression analysis, similar results were obtained as when using logistic regression analysis (online suppl. Table 3): model 1 HR 6.28 (95% CI 2.92–13.50); model 2 HR 6.08 (95% CI 2.83–13.08); model 3 HR 2.21 (95% CI 0.70–6.95); and model 4 HR 2.31 (95% CI 0.73–7.29). Figure 3 shows the estimated CIF for ESRD comparing adoptees with affected (ESRD) biological parents with unaffected biological parents. According to Gray's test (p value <0.0001), the CIF of ERSD is significantly different between adoptees with and without an affected parent.

Table 2. Prevalence of diabetes mellitus, hypertension, glomerulonephritis, and mortality among study participants with and without ESRD any time during follow-up (1964–2012)

	No ESRD	ESRD	*p* value*
Adoptees, *n*	37,375	111	
Diabetes mellitus	1,800 (4.82)	56 (50.45)	<0.0001
Hypertension	3,552 (9.50)	77 (69.37)	<0.0001
Glomerulonephritis	150 (0.40)	25 (22.52)	<0.0001
Mortality	2,033 (5.44)	39 (35.14)	<0.0001
Biological parents, *n*	58,890	397**	
Diabetes mellitus	7,985 (13.56)	181 (45.59)	<0.0001
Hypertension	14,814 (25.16)	274 (69.02)	<0.0001
Glomerulonephritis	254 (0.43)	82 (20.65)	<0.0001
Mortality	27,209 (46.20)	316 (79.60)	<0.0001
Adaptive parents, *n*	63,676	463	
Diabetes mellitus	8,483 (13.32)	161 (34.77)	<0.0001
Hypertension	17,631 (27.69)	317 (68.47)	<0.0001
Glomerulonephritis	297 (0.47)	98 (21.17)	<0.0001
Mortality	37,766 (59.31)	378 (81.64)	<0.0001

* Both Fisher exact test and chi-square test.
** One adopted offspring had 2 biological parents with ESRD.
Values are *n* (%). ESRD, end-stage renal disease.

Table 3. Results for the cohort study for ESRD among Swedish-born adoptees with an affected biological (or adoptive parent) compared with those without an affected biological (or adoptive) parent

Risk factors	Biological parents		Adoptive parents	
	model 1^{+}	model 2$^{\#}$	model 3^{+}	model 4$^{\#}$
ESRD (in parents)	6.40 (2.96–13.85)	6.41 (2.96–13.89)	2.23 (0.71–7.05)	2.40 (0.76–7.60)
Year of birth	0.96 (0.94–0.98)	0.96 (0.94–0.98)	0.96 (0.94–0.98)	0.96 (0.94–0.98)
Gender (reference male)	0.78 (0.53–1.13)	0.81 (0.55–1.18)	0.78 (0.53–1.13)	0.81 (0.56–1.19)
County	1.01 (0.98–1.03)	1.01 (0.98–1.03)	1.01 (0.98–1.03)	1.01 (0.98–1.03)
Education	0.71 (0.55–0.91)	0.76 (0.59–0.98)	0.71 (0.55–0.91)	0.75 (0.59–0.97)

ESRD, end-stage renal disease; $^{+}$ Crude model = univariate model for each variable = model 1 and 3; $^{\#}$ multivariate model = model 2 and 4 (all variables included in the model).

Case-Control Study

The results of the case-control study are presented in Table 4. ESRD in the adoptees was significantly associated with ESRD in biological parents with an OR of 6.00 (95% CI 1.83–19.60) in adoptees with an affected biological parent. ESRD in an adoptive parent was not significantly associated with ESRD in adoptees, OR 1.25 (95% CI 0.14–11.18). Thus, the estimates in the case-control design (Table 3) are not majorly different from those of the cohort design presented in Table 2.

Heritability

The heritability ($h^2 \pm$ SE) for ESRD was $h^2 = 59.5 \pm 18.2\%$ with Falconer's regression [47]. The heritability was also examined in the case-control study with a range of different estimates of the prevalence of ESRD (Table 5) [45]. The results are presented in Table 5. The heritability varied from 40% in a population with 0.01% prevalence to 67% in a population with 2% prevalence. With a prevalence of 0.60% (Table 1), as in the current study population, the heritability was 57%, which is similar to that obtained using Falconer's regression [47].

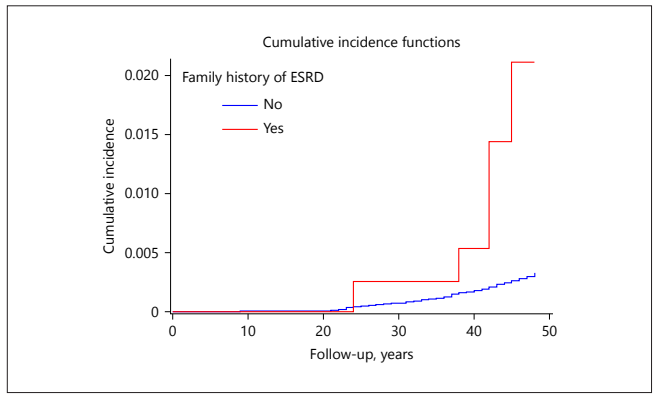

Fig. 2. The estimated CIF for ESRD comparing adoptees with affected (ESRD) bio-logical parents with unaffected biological parents. According to Gray's test (p value <0.0001), the CIF of ERSD is significantly different between adoptees with and with-out an affected parent. CIF, cumulative in-cidence functions; ESRD, end-stage renal disease.

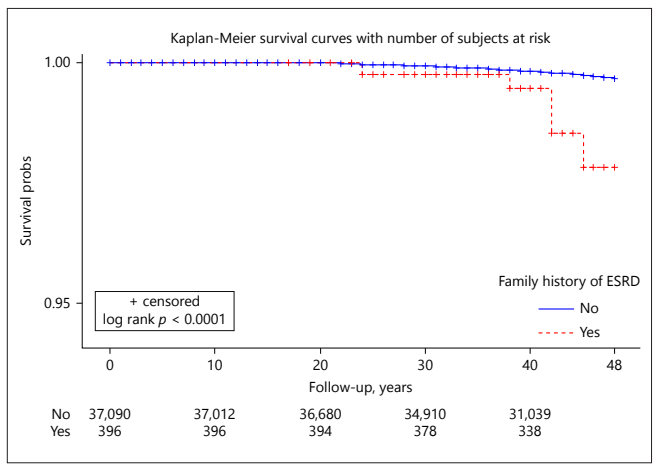

Fig. 3. ESRD-free survival curves. Kaplan-Meier analysis comparing adoptees with affected (ESRD) biological parents with unaffected biological parents. The log-rank test (p value <0.0001) indicates that differ-ences between the groups are statistically significant. ESRD, end-stage renal disease.

Sensitivity Analysis

We performed a sensitivity analysis with both adoptive parents "known" to determine the robustness of results and to assess the effect of lack of information about adoptive child status (i.e., the child did not grow up with one of their biological parents).

In online supplementary Tables 4 and 5 we show the results of the Cohort and Case-Control studies. Data about adoptees with adoptive parents revealed even higher familial risks.

Discussion

The high heritability of ESRD in the present study indicates that genetic factors are crucial risk factors causing ESRD in the Swedish population. Shared familial environmental factors did not contribute significantly. This study confirms the findings of previously conducted family studies that showed strong familial clustering of ESRD [6–28]. However, the present adoption study is actually an extension of previous studies, which indicated that genetic fac-

Table 4. Results of the matched case control study (1:5). For ESRD among adoptees with an affected biological or adoptive parent

ORs for ESRD in adoptees with an affected biological parent*	6.00 (1.83–19.66)
ORs for ESRD in adoptees with an affected adoptive parent*	1.25 (0.14–11.18)

Data are presented as OR 95% CI. ESRD, end-stage renal disease.
* Cases (n = 86) and controls (n = 430).

Table 5. Heritability (h^2) of ESRD based on estimated population prevalence and tetrachoric correlation in case-control study according to Frisell et al. [45]

Exposed cases	Unexposed cases	OR	Prevalence	Tetrachoric correlation	Heritability, %
6	80	6.00	0.01	0.20	40
6	80	6.00	0.05	0.226	45
6	80	6.00	0.1	0.24	48
6	80	6.00	0.5	0.28	56
6	80	6.00	1.0	0.306	61
6	80	6.00	1.5	0.32	64
6	80	6.00	2.0	0.334	67

Heritability (h^2) = the proportion of variance that is due to hereditary factors. ESRD, end-stage renal disease.

tors, and not only shared familial environmental factors, play an important role in the familial transmission of ESRD. Previously, a twin study (the Vietnam Era Twin Registry) by Raggi et al. [48] has shown a heritability of 50% for estimated glomerular filtration rate. Another twin study by Arpegård et al. [49] estimated the heritability of Cystatin C (60%) and creatinine (59%). No twin study that formally determines heritability (h^2) of ESRD has been published thus far and so this is the first study estimating the heritability of ESRD. The high heritability for ESRD in the present study is similar to the heritability estimated for different measures of kidney functions [48, 49]. We therefore do not believe that our results overestimate the heritability of ESRD because severe phenotypes are often more heritable than less severe phenotypes such as the measure of kidney function in a cohort of twins. The high heritability of ESRD suggests that gene hunt studies for common genetic variants may be worthwhile. Our results are in line with the recent rapid progression of genome-wide association studies (GWAS) of various kidney traits and disorders [50]. Genetic studies, used to investigate traits that define CKD, such as estimated glomerular filtration rate or urinary albumin/creatinine ratio, have identified more than 50 associated genomic regions [49]. Most interestingly, genomic regions identified in GWAS of CKD-defining traits partly overlap with the causal genes for monogenic kidney diseases. GWAS research on kidney function traits may therefore provide knowledge about the more severe forms of kidney diseases [50]. However, until all genetic variants associated with kidney disease and ESRD are discovered, family history will continue to be important. The present study show that shared genes contribute intensively to familial risks and that the family history of ESRD may signal an increased genetic risk of ESRD.

Many ESRD registries have an ascertainment bias because older patients who receive conservative care for ESRD are not included. The adoptee cohort in the present study is relatively young so this issue is avoided, which is a strength of the present study. Another strength of the study is that the family history of ESRD is defined by NPR diagnosis and not by self-report. Self-report and recall bias are common problems associated with many family history studies [39]. At the same time, the use of register-based data is a potential source of error. We do not know how the diagnosis of ESRD was established. We therefore used the definition of dialysis or transplantation (i.e., in active uremic care) to secure high validity. Patients with ESRD in Sweden are usually diagnosed and treated by specialists in nephrology. Moreover, there is a high validity of diagnosis in the Swedish hospital register ranging from 85

to 95% for many diagnoses [38]. The Swedish NPR concurs with the Swedish Renal Register (SRR) in terms of ESRD [51, 52]. The SRR has been extensively used and, when validated, the authors found that information of >95% of persons with ESRD had entered the SRR [51, 52]. Moreover, the used registers are almost complete and have successfully been used to estimate familial risks for a number of diseases [35–41]. Another limitation is that we had no information about the age at which children were adopted, although it is likely that most adoptions occurred during early childhood. According to previous studies, a majority of children were adopted before 12 months of age [53, 54]. The present adoption study included only adoptees who were born in Sweden. We therefore cannot generalize the present study and apply its findings to a population of non-European origin.

To summarize, the heritability of ESRD is high, and this indicates that genetic factors are important in assessing the etiology of ESRD among the Swedish population. Further, gene hunt studies could be worthwhile. Moreover, ESRD in a biological parent is an important risk factor for causing ESRD.

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Ethics Statement

The study was approved by the Ethics Committee of Lund University, Sweden, and was performed in compliance with the Helsinki Declaration. The Ethics Committee waived informed consent as a requirement because the researchers received only coded data.

Disclosure Statement

The authors have no conflicts of interest to declare.

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