Immunoglobulin A nephropathy and disease complications – register-based studies

To all my patients with glomerular diseases
and your like across the world.

Örebro Studies in Medicine 275

SIMON JARRICK

Immunoglobulin A nephropathy and disease complications
– register-based studies

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Abstract

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Immunoglobulin A nephropathy (IgAN) is the commonest primary glomerular disease worldwide. A kidney biopsy is required for the diagnosis. IgA immune-complex depositions sets off a cascade leading to renal scarring, proteinuria and hypertension. Peaking in young adults, IgAN contributes significantly to the burden of chronic kidney disease, which in turn may lead to cardiovascular disease and death. As IgAN peaks in childbearing age, its effect on pregnancy outcomes is of interest.

All studies use the same cohort of 4126 patients with a biopsy diagnosis of IgAN, identified through the combination of computerized and manual search in biopsy reports from all Swedish kidney pathology labs. In study I, a random subset of 127 patients from the biopsy cohort were selected for diagnosis validation by patient chart review. IgAN was confirmed or likely in 121 cases (positive predictive value > 95 %). Mean age at diagnosis was 39.6 years, 74 % were male.

Study II compared mortality in IgAN patients and an individually matched reference population by survival analysis. IgAN was associated with an increase of 53 % in all-cause and 59 % in cardiovascular mortality, with an absolute excess death rate of in 310 person years. Mortality before end-stage renal disease was not significantly increased.

Study III used a similar design to examine incident fatal and non-fatal ischemic heart disease (IHD) in IgAN patients and the same reference populations. We found an 86 % increase in IHD hazard and an absolute excess IHD risk of one per 340 person-years.

In study IV, outcomes of 327 pregnancies in 208 women with IgAN were compared to reference pregnancies without IgAN, indicating increased odds of preterm birth < 37 weeks gestation, but not for very preterm birth < 34 weeks. Preeclampsia odds were quadrupled. Stillbirth and neonatal death were both uncommon and not increased in IgAN.

Keywords: immunoglobulin A nephropathy, nephrology, validation studies, register studies, cohort studies, mortality, ischemic heart disease, pregnancy, preterm birth.

Simon Jarrick, School of Medicine
Örebro University, SE-701 82 Örebro, Sweden,
simon.jarrick@regionorebrolan.se

Original articles

This thesis is based on the following papers, which are referred to in the text by Roman numerals (I-IV), reproduced with permission:

I. **Clinical validation of immunoglobulin A nephropathy diagnosis in Swedish biopsy registers.** Jarrick S, Lundberg S, Welander A, Fored CM, Ludvigsson JF. Clinical Epidemiology. 2017 Jan 31;9:67-73. doi:10.2147/CLEP.S118730. eCollection 2017. PMID: 28203107. *Originally published by and used with permission from Dove Medical Press Ltd.*

II. **Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study.** Jarrick S, Lundberg S, Welander A, Carrero JJ, Höijer J, Bot-tai M, Ludvigsson JF. J Am Soc Nephrol. 2019 May;30(5):866-876. doi: 10.1681/ASN.2018101017. Epub 2019 Apr 10. PMID: 30971457

III. **Immunoglobulin A nephropathy and ischemic heart disease: a nationwide population-based cohort study.** Jarrick S, Lundberg S, Sundström J, Symreng A, Warnqvist A, Ludvigsson JF. BMC Nephrol. 2021 May 5;22(1):165. doi: 10.1186/s12882-021-02353-7. PMID: 33952193

IV. **Pregnancy outcomes in women with immunoglobulin A nephropathy: a nationwide population-based cohort study.** Jarrick S, Lundberg S, Stephansson O, Symreng A, Bottai M, Höijer J, Ludvigsson JF. J Nephrol. 2021 Mar 8. doi: 10.1007/s40620-021-00979-2. PMID: 33683676

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List of Abbreviations

ACEi = angiotensin converting enzyme inhibitor
ACR = urine albumin to creatinine ratio
AER = urine albumin excretion rate
ARB = angiotensin II receptor blocker
C3 = complement factor 3
CDR = the Swedish Cause of Death Register
CKD = chronic kidney disease,
ESRD = end-stage renal disease,
GFR = glomerular filtration rate
eGFR = estimated GFR (calculated from creatinine or cystatin C)
GN = glomerulonephritis
HR = hazard ratio
aHR = adjusted hazard ratio
IgA = immunoglobulin class A
IgA1 = immunoglobulin class A subclass 1
gd-IgA1 = galactose deficient immunoglobulin IgA1
IgAN = immunoglobulin A nephropathy,
IgAV = immunoglobulin A vasculitis, Henoch-Schönlein purpura
IgG = immunoglobulin class G
IHD = ischemic heart disease
MBR = the Swedish Medical Birth Register
NPR = the Swedish National Patient Register
OR = odds ratio
PCR = urine protein to creatinine ratio
PDR = the Swedish Prescribed Drugs Register
PE = preeclampsia
PID = Swedish 10 digit personal identity number
PY = person-years
RAASi = renin-angiotensin-aldosterone system inhibitor
RRT = renal replacement therapy (dialysis or kidney transplantation)
TPR = the Swedish Total Population Register

Introduction

Immunoglobulin A nephropathy (IgAN)

IgA nephropathy is a form of chronic glomerulonephritis (GN), i.e. an inflammatory disease affecting the glomeruli of the kidneys, leading to various degree of renal damage resulting in hematuria, proteinuria, impaired glomerular filtration and hypertension. As there is no pathognomonic clinical picture for IgAN, a renal biopsy is required for diagnosis, and for distinguishing IgAN from other glomerular diseases with a similar clinical presentation. The histopathological hallmarks are signs of glomerular inflammation with the proliferation of mesangial cells, and the demonstration by immunofluorescence or immunohistochemistry of deposits of immunoglobulin A (IgA) within the glomerular mesangium.

Brief historical remarks

When the French pathologists Jean Berger and Nicole Hinglais a little more than 50 years ago first described intercapillary deposits of IgA in the renal biopsies of 25 patients, they changed the history of nephrology.[1] The case series was presented in 1968 in a brief and rather anonymous paper in the *Journal d'Urologie et de Néphrologie*. Their discovery relied on the emerging immunofluorescence technique, which allowed them to demonstrate a consistent pattern of diffuse subendothelial deposits of IgA, and to a lesser extent immunoglobulin G (IgG) and complement protein C3, in the glomerular mesangium of all glomeruli. The light microscopic changes were quite variable, with increase of glomerular mesangial cells in mainly in a focal segmental pattern. All the patients had microscopic hematuria and low-grade proteinuria, about half had a history of macroscopic hematuria, usually following an acute throat infection, and only three had significant hypertension.

The disease, first identified as Berger's disease, was at first considered generally benign or slowly progressing. With time, some patients progressed to end-stage renal disease (ESRD). As more cases were identified around the world, including in patients undergoing renal biopsies in the investigation of advanced renal disease, it became clear both that the disease can severely impact kidney function, and that the disease is not uncommon.[2] Today, Berger's disease, known as IgA nephropathy or IgA nephritis (IgAN), is recognized as the commonest glomerulonephritis over the world,[3, 4] contributing significantly to the global burden of chronic kidney disease, with estimates

of IgAN responsible for some 4-10 % of all patients requiring renal replacement therapy (RRT) worldwide.[5, 6]

Clinical presentation and natural history

The archetypical presentation of IgAN is that of a young male presenting with gross hematuria, recurring at irregular intervals, typically in the setting of a sore throat or some other upper airway infection, with microscopic hematuria and proteinuria persisting between relapses.[3] The clinical picture is however highly variable and this typical manifestation may be seen in some 20-40 % of the cases.[7-10] Many patients are identified through the presence of microscopic hematuria in routine dipstick urinalysis, either incidentally in hypertension workup, or in school or occupational screening programs. As both screening policies and the threshold for renal biopsy may differ among countries and regions, so does the proportion identified with subclinical disease.[11] Japan practices a nation-wide glomerulonephritis screening program, with routine urine dipstick in all school children since the seventies and in adult workers since the eighties, resulting in a higher proportion of patients with mild disease at diagnosis.[12] A small proportion present with acute renal failure due to rapidly progressive glomerulonephritis with crescent formation, or on rare occasions with the nephrotic syndrome with massive proteinuria, low plasma albumin and edema. Most of the remaining cases are found in predominantly older patients with manifest proteinuria, hypertension and renal impairment.[13]

Whereas some patients may retain subclinical disease for years or decades, most adults with IgAN develop chronic kidney disease (CKD) of some degree, with increasing proteinuria and hypertension, renal scarring and progressive loss of renal filtration capacity. In most cohorts studied, about 13-23 % of patients with apparent debut in adulthood will reach ESRD within 10 years, and 33-36 % within 20 years from diagnosis,[9, 14, 15] relying on renal replacement therapy (RRT) for their survival. Complete remission of IgAN, defined as resolution microscopic hematuria and insignificant proteinuria for six months or more, is generally considered to be rare in adult patients, although there is a shortage of studies addressing this question. On the contrary, in a recent study following 62 IgAN patients with conservative treatment (no immunosuppression) for a minimum of 5 years (median 9.9 years), remission (< 5 erythrocytes per high power field and a urine protein to creatinine ratio < 34 g/mol, corresponding to an ACR around 11 g/mol[16]), was achieved by 19 (30.6 %). Remission was mainly seen in

patients with low grade proteinuria (urine protein to creatinine ratio < 56 g/mol) at IgAN diagnosis.[17]

Higher risk of progression has been linked to both clinical and histopathological features. The presence of hypertension, proteinuria > 1 g/24h and reduced estimated glomerular filtration rate (eGFR) at disease presentation have all been tied to higher risk of progression to ESRD, although not precise enough to make reliable forecasts at the individual level.[18-20] A histological grading system has been developed (Oxford-MEST), based on the findings in biopsy of mesangial proliferation (M), endocapillary proliferation (E), segmental glomerulosclerosis (S) and tubular atrophy and interstitial fibrosis (T). Especially the T score is associated with high risk of eGFR decline as it is a marker of irreversible renal damage, whereas the E score does not appear to add prognostic information.[21] More recently, an IgAN prognostic tool has been developed combining clinical and histopathological data.[22] This tool has been evaluated in multi-ethnic cohorts and resulted in better discriminatory power compared to clinical and histological models alone.[23]

Epidemiology of IgAN

Immunoglobulin A nephropathy is now recognized as the commonest primary glomerulonephritis worldwide. Annual incidence rates of 2-10 per 100,000 have been reported in adults,[11, 24-29] with notable differences between countries. Genetic differences between ethnical groups have been proposed, though there is evidence that detection bias might explain at least some of the variation.[4, 11, 30] Disease severity varies and many cases are discovered in asymptomatic individuals, either by population based screening programs, by urinalysis in high-risk groups such as patients with hypertension, or incidentally in patients seeking care for other reasons. Therefore, detection rates are highly influenced by regional differences in screening and renal biopsy policies. A Japanese study based on general school screening of more than 270,000 children found an incidence of 4.5 per 100,000 person-years (py) in children 6-15 years. Autopsy studies have shown rates of mesangial IgAN deposits in kidney necropsies of 4.8-6.9 % of patients without a prenatal IgAN diagnosis, with morphological (such as mesangial proliferation) or clinical (hematuria or proteinuria) signs of glomerulonephritis present in approximately 1 %.[31, 32] Similarly, IgA deposits have been found in the mesangium of 6-32 % of donor kidneys at the time of renal transplantation.[33-35] Such incidentally discovered IgA deposits not always represent early stages of IgAN, and their significance is not fully understood.

Pediatric IgAN and systemic IgA vasculitis (Henoch-Schönlein purpura)

Whereas most cases are diagnosed in early adulthood, IgAN may also affect children. This most commonly occurs in the context of systemic IgA vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP). This is an acute onset autoimmune vasculitis, engaging small blood vessels predominantly in the skin, joints, gut and kidney, mainly affecting children between 3 and 15 years. The annual incidence has been estimated at around 12-29 cases per 100,000 children, with a peak incidence of 24-70 per 100,000 in children per year between 4 and 6 years' age.[36-38] The incidence in adults is typically 0.8-1.8 per 100,000 py.[37] The disease is characterized by the acute onset of palpable purpura (bruise marks) appearing mainly on the lower legs and buttocks, often a few days after a viral infection. In addition, there may be arthritis or non-specific arthralgia and diffuse abdominal pain with or without gastrointestinal bleeding. Renal involvement has been reported in 20-54 %, with higher frequencies in older children and adults.[39-44] The histopathological pattern of renal IgAV is indistinguishable from IgAN confined to the kidneys, as described by Berger et al already in 1971.[45] The clinical picture of IgAV nephritis ranges from isolated microscopic hematuria with or without mild proteinuria (< 1 g/day), or isolated proteinuria, to nephritic or combined nephritic-nephrotic syndrome. Children typically encounter mild renal disease; in a meta-analysis including 12 studies and 1133 children, 34 % developed abnormal urinalysis; out of the 79 % with only hematuria with or without mild proteinuria, only 1.6 % developed long-term renal impairment, whereas the same was seen in 20 % among the 21 % with nephritic or nephrotic syndrome.[42]

Also when pediatric IgAN is limited to the kidneys, most studies report a favorable prognosis in children compared with adults. The risk for ESRD has been estimated to 7-9 % at 10 years and 13-20 % at 20 years from diagnosis.[46, 47] A Japanese study found a high rate of spontaneous remission in 96 pediatric patients with untreated IgAN, at 57 % 5 years and 77 % 10 years from disease onset, although recurrence of the disease was seen in 32 % 10 years after remission[48]. The difference compared to adult IgAN might reflect that pediatric IgAN to a higher degree represent early stages, and one should also bear in mind that children with progressive IgAN may end up with ESRD early in life, thus depending on renal replacement therapy for many decades.

Pathophysiology of IgAN

Since the first description of IgAN in 1968, much effort has been made to clarify the process leading to mesangial IgA depositions, cell proliferation and renal scarring. In the last decades, it has become evident that there is not one single pathological mechanism, but rather a series of key events or "multiple hits", where both genetics and environmental factors play a role.

A few observations strongly suggest that the disease process starts outside the kidney. Firstly, there is a high rate of recurrence of IgAN after kidney transplantation, a fact observed by Berger et al already in 1975.[49, 50] Secondly, the disappearance of IgA deposits have been observed in kidneys with IgAN, transplanted into non-IgAN transplant recipients.[51] Thirdly, onset of IgAV/HSP as well as clinical relapses of IgAN with macroscopic hematuria regularly follow upon upper airway infections. Finally, IgA phenotype with defective carbohydrate structure has been found in high levels in the circulation if IgAN patients[52] and in patients with IgAV with later renal involvement,[53] as well as in first grade relatives to IgAN patients. The following pathogenic events or "hits" have been identified:[54]

1. **Hereditary increase in the circulating levels of galactose-deficient polymeric IgA1.** Serine and threonine amino acids in the hinge region of IgA1-molecules can link carbohydrate chains containing N-acetylgalactosamine and galactose (*O*-glycosylation). Normally, circulating IgA1 is mainly secreted from B-lymphocytes within the bone-marrow, typically monomeric and rich in galactose. In contrast, mucosal IgA1 synthesized by peripheral B-lymphocytes in the mucosa-associated lymphoid tissues (MALT) is typically di- or polymeric and poor in galactose. It is believed that in IgAN, B-lymphocytes migrating from the MALT to the bone barrow release mucosal-type galactose-deficient polymeric IgA1 (gd-IgA1) into the bloodstream. As increased gd-IgA1 is also seen in healthy relatives to IgAN patients, this step alone is not sufficient to cause IgAN.
2. **Circulating antibodies of IgA or IgG-class directed against gd-IgA1.** The gd-IgA1 has the ability to provoke an immune response, resulting in the release of IgG- or IgA-antibodies, possibly by a molecular mimicry mechanism, where galactose deficient *O*-glycans might resemble bacterial or viral call wall glycoproteins and hence activate B-lymphocytes. Exposure to virial antigens in the upper airways and gastrointestinal tract are thought to play a role.

3. **Formation of IgG-gd-IgA1-immune complexes**. The formation of immune-complexes is critical, as gd-IgA1 is not alone sufficient to cause mesangial cell proliferation. Immune-complexes may form either in the circulation or as an immune response to gd-IgA that has been entrapped in the glomerular mesangium and a reduced clearance of immune complexes by macrophages.
4. **Activation of mesangial cells, glomerular injury and scarring.** This hit contains the binding of gd-IgA-containing immune complexes to transferrin receptors on mesangial cells and to Fc-alpha-receptors (CD89), and possibly a reduced clearance of immune complexes from macrophages.

The development of renal inflammation and injury in IgAN likely depends on a combination of genetic and environmental factors. Indeed, the great variation in presentation and clinical course may indicate that there IgAN could be treated rather as a clinic-pathological syndrome with several common features, rather than a single disease process. It has also been disputed whether kidney-restricted IgAN and the glomerulonephritis of systemic IgAV are two faces of the same disease, or should be considered two separate entities.[55-57]

Chronic kidney disease

The 2012 updated criteria from Kidney Disease: Improving Global Outcomes (KDIGO) defined chronic kidney disease (CKD) as having "abnormalities of kidney structure or function, present for > 3 months, with implications for health".[58] The KDIGO criteria further specify:

Markers of kidney damage (≥ 1 for > 3 months)
Albuminuria (AER ≥ 30 mg/d; ACR ≥ 30 mg/g (≥ 30 mg/mmol creatinine)
Urinary sediment abnormalities
Electrolyte and other abnormalities due to tubular disorders
Abnormalities detected by histology
Structural abnormalities detected by imaging
History of kidney transplantation
Decreased glomerular filtration rate (GFR) (for > 3 months)
GFR < 60 mL/min per 1.73 m^2 (GFR categories G3a-G5)

Table 1. Criteria for chronic kidney disease. AER = urine albumin excretion rate, ACR = urine albumin to creatinine excretion rate, GFR = glomerular filtration rate. Reproduced from reference[58]

Renal impact may be classified be the degree of GFR impairment:

GFR category	GFR (mL/min/1.73m^2)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

*Relative to young adult level.
In the absence of kidney damage, neither G1 nor G2 fulfill the criteria for CKD

*Table 2. *Relative to young adult level. Reproduced from reference[58]*

More recently, KDIGO has proposed a two-axis classification including both GFR and proteinuria, in order to better predict renal prognosis:

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m2) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased*	60 – 89			
	G3a	Mildly to moderately decreased	45 – 59			
	G3b	Moderately to severely decreased	30 – 44			
	G4	Severely decreased	15 – 29			
	G5	Kidney failure	< 15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1. Reproduced from KDIGO reference[58]

Recently, the Global Burden of Disease, Injuries, and Risk Factors Study estimated the global prevalence of CKD in 2017 to 9.1 %, equaling around 700 million cases worldwide and responsible for around 2.6 million deaths and the loss of 36 million disability-adjusted life-years (DALYs), mainly due to its impact on cardiovascular disease. Among CKD cases, early stages (G1-G2) accounted for 5 %, G3 for 3.9 %, G4 for 0.16 % and G5 (ESRD) for 0.07 % of the global population. The prevalence of dialysis or kidney transplantation was estimated to a total 0.041 % and 0.011 % respectively.

The risk of progression to ESRD with the need for RRT by dialysis or transplantation varies, and depends on primary renal diagnosis, age at diagnosis, and the rate of hypertension and proteinuria at diagnosis and during follow-up. Globally, the most common causes for CKD and ESRD are diabetes, mainly type 2, and hypertension, with glomerulonephritis accounting for a smaller proportion. However, the panorama shows great variations between countries and regions. According to the European Renal Association and European Dialysis and Transplantation Associations (ERA-EDTA) 2019 registry report, GN accounted for 11 % of all patients starting RRT (incident RRT) in 2019, ranging from 7 % in Bosnia and Herzegovina to 21 % in Iceland. As GNs tend to strike at lower ages, their proportion among incident ESRD was 7 % among those older than 65 years and 16 % among younger patients. Thus, among all patients undergoing RRT (prevalent RRT), the proportion of GN as primary diagnosis is higher, in Europe constituting 19 % and in Sweden 25 %, as such the leading cause of RRT. A compilation by the Swedish Renal Registry of more than 21,000 patients starting RRT between 1991 and 2010, IgAN or IgAV was the primary renal diagnosis in at least 4.2 % of the cases. The true proportion is likely higher, as another 5.8 % of the patients were classified as "glomerulonephritis, histologically not examined", and IgAN representing approximately one third of all GNs in Swedish biopsy registers.[5, 59]

Treatment of IgAN

The optimal treatment regime in IgAN has long been controversial. While there is wide agreement on the benefits of optimal supportive care, including strict control of blood pressure and proteinuria and modifying life-style in a disease non-specific kidney-protective manner, the role of immunosuppression is still under debate. As there is evidence of IgAN being having autoimmune features, many immune-modulating strategies have been evaluated in its treatment, including systemic glucocorticoids, other immuno-

suppressive drugs and tonsillectomy.[60] With the great variation in IgAN severity and prognosis, there is no "one size fits all"; rather a tailored approach based on clinical and histopathological has been advocated, as summarized by the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[61]

Supportive care

In addition to glomerular filtration rate (GFR) at diagnosis, hypertension and proteinuria are the best predictors of disease progression and ESRD, and should be the first to be addressed therapeutically.

Proteinuria and blood pressure control

Renin-angiotensin-aldosterone system inhibitors (RAASi), including angiotensin converting enzyme inhibitors (ACEi) and angiotensin-II-receptor blockers (ARB) have been shown to lower blood pressure, decrease proteinuria and slow GFR decline in adult IgAN patients,[62] and are currently recommended to all IgAN patients with either hypertension or proteinuria > 0.5 g/day (or a spot urine albumin creatinine ratio (ACR) of approximately > 30 g/mol). Even when blood pressure is within optimal limits (< 120 mmHg in adults; in children < 90th percentile for sex, age and height, optimally < 50th centile), as long as there is residual proteinuria, RAASi should be increased to maximum tolerated dose, as remission of proteinuria is associated with better outcome.[63] If this is not achieved, the addition of non-dihydropyridine calcium channel blockers, beta-adrenoceptor antagonist or aldosterone antagonist is recommended. Dual RAASi with the combination of an ACE and an ARB is not recommended, as this in a recent large cohort was associated with higher proteinuria at end of follow-up, with no benefits for overall renal function.[64]

Sodium-glucose transporter-2 inhibitors

Sodium-glucose transporter-2 (SGLT2) inhibitors are a relatively new class of drugs that specifically inhibit glucose reuptake in the renal tubules. A recent randomized controlled study of the SGLT2 inhibitor dapagliflozin including more than 4200 patients showed a reduction in proteinuria and eGFR decline, as well as in cardiovascular disease and all-cause mortality, in proteinuric CKD patients with and without diabetes.[65-68] A subgroup of 270 IgAN patients showed a 26% reduction in albuminuria and a small but significant reduction in eGFR decline during a median follow-up of two

years.[69] An ongoing study addresses the effects of empagliflozin in CKD patients with or without proteinuria, including 817 patients with IgAN.[70]

Statins

There is some evidence that dyslipidemia is associated with renal function decline in IgAN patients.[71] However, data on lipid lowering agents in IgAN patients are limited to one small open-label observational study.[72]

Life-style modification

A dietary restriction in sodium hos proved beneficial in controlling hypertension in IgAN patients.[73] Studies on the contribution of obesity to the progression of IgAN have shown conflicting results.[74] However, taking into account the well-established associations between obesity, hypertension, proteinuria and renal damage, lifestyle changes promoting normal weight and physical activity is generally recommended.[60, 61]

Disease modifying treatments

Immune suppressing drugs including systemic glucocorticoids

The role of glucocorticoids in IgAN is still under debate. With strong indications of IgAN being an autoimmune disorder, glucocorticoids and other immune-modulating agents would appear a natural strategy. Indeed, a few randomized controlled studies and a consequent meta-analyses examining steroid therapy in proteinuric IgAN has demonstrated beneficial effects both in reducing proteinuria and in limiting the decline in GFR.[75-77] This has not been shown in IgAN with less proteinuria, and larger retrospective studies indicate that IgAN patients with proteinuria less than 1 g / 24 h or eGFR > 60 mg/mL/1.73m^2 are less likely to benefit from steroid treatment.[78, 79] Additionally, the more recent German STOP IgAN trial did demonstrate transient reduction in proteinuria but no reduction in eGFR decline from corticosteroid monotherapy (eGFR ≥ 60 mL/min) or a combination of corticosteroids with cyclophosphamide and azathioprine (eGFR < 60 mL/min) in patients after optimized optimization of supportive care, even after 10 years' follow-up. The Japanese TESTING trial, comparing oral methylprednisolone with placebo, was terminated early after the inclusion of 262 out of intended 750 IgAN patients, because of high rates of severe adverse effects in the treatment arm, mainly infections. The treatment showed significant effect on eGFR decline and proteinuria.[80]

Therapies addressing B-lymphocytes have shown conflicting results. Mycophenolate mofetil treatment has been associated with reduced eGFR decline and proteinuria in Chinese IgAN patients, with fewer adverse effects than and might be considered as a steroid sparing agent to reduce corticosteroid adverse effects. European studies have shown conflicting results.[60] Rituximab is a recombinant monoclonal antibody that binds to CD20-antigen on B-lymphocytes. It has been evaluated in small studies on IgAN[81] and IgAV[82, 83] in combination with ACEi, with no beneficial effects on proteinuria, eGFR or gd-IgA1 levels and is currently not recommended.

Among calcineurin inhibitors, cyclosporine has shown discouraging results.[84] One meta-analysis indicates that tacrolimus in combination with corticosteroids might reduce proteinuria, but no difference in renal function tests.[85]

Topical steroids

With increasing theoretical and epidemiological evidence that gut associated lymphoid tissue may play an important role of in the production of gd-IgA1 and immune activation in IgAN, this has also emerged as a target of immunomodulatory treatment. Topical release formulations of the local acting glucocorticoid budesonide have shown to reduce proteinuria and slow eGFR decline in IgAN patients on optimal supportive care including ACEi och ARB treatment, compared to placebo, although long term data are still lacking.[86-88] Retrospective data suggest that the treatment effect may be comparable or possibly even superior to systemic steroids.[89]

Tonsillectomy

Since bouts of macroscopic hematuria in IgAN are linked to upper airways infection and the galactose deficient IgA1 presents in the renal mesangium of IgAN kidneys is abundant in tonsillar tissue, tonsillectomy has been proposed as a treatment to reduce relapses and slow down IgAN progression. Current evidence based mainly on retrospective studies indicate that tonsillectomy may improve renal outcomes in Japanese IgAN patients with a high risk of disease progression.[90] European data are limited to 41 propensity score matched pairs retrospectively evaluated in the VALIGA study, and do not support tonsillectomy in a Caucasians.[91]

Mortality

While CKD confines a recognized risk factor for death, mortality in patients with IgAN has been studied only to a limited extent, and there have been no large studies comparing IgAN patients to a matched reference population. Absolute excess mortality has not been examined in IgAN patients.

Large epidemiological studies of all-cause CKD demonstrate higher risk of death and ESRD across all ages with higher CKD level, whether defined by increasing albuminuria or decreasing GFR, even at moderate reduction in GFR, with the number of observed deaths widely exceeding progressions to ESRD.[92, 93] As these studies include patients with CKD from all causes including kidney disease secondary to diabetes and hypertension, these results may not be valid for patients with IgAN and other GN. A few studies have demonstrated higher risks for ESRD than for death in patients with primary glomerular diseases during median follow-up times of up to of ten years.[94, 95]

Hajeong Lee et al examined death and ESRD progression in 1364 IgAN patients followed for a median of eight years in a single-center setting in Seoul, Korea. Patient survival rates was 96 % and 91.8 % ten and twenty years from renal biopsy; few patients were followed more than 30 years. Of 71 deaths, 39 occurred before progression to ESRD. Standardized mortality ratio (SMR) was calculated using sex-adjusted census data divided into 5-year age and calendar year categories, and was 1.43 (1.04-1.92) for all patients. Higher mortality was seen with eGFR < 60 mL/min/1.73m^2, proteinuria ≥ 1 g/day or hypertension with systolic blood pressure ≥ 140 mmHg. A low-risk group including patients with none or one of these risk factors had an SMR close to one, i.e. no increased mortality compared to the general population.[8] Progression to ESRD was a strong predictor of mortality. In another study comparing different primary glomerulopathies, IgAN patients had significantly better patient survival compared with patients with membranous nephropathy, focal segmental glomerulosclerosis and membranoproliferative GN, despite similar or higher ESRD progression rates.[94] The same authors studied separately 153 patients with IgAN that was clinically benign at time of biopsy (eGFR ≥ 60 mL/min/1,73m^2, proteinuria < 0.5 g/day or urine protein to creatinine ratio (PCR) < 56 g/mol, median systolic blood pressure 120 mmHg), with a median follow-up of 7.9 years. Six patients progressed to ESRD within 5 to 19 years and four died, three before ESRD for unknown reasons or reasons not related to kidney disease, one possibly attributable to IgAN, 11.8 years after progression to ESRD and start of dialysis.[96]

In a Norwegian nation-wide study based on quality register data, Thomas Knoop et al followed 633 patients with IgAN. During a median follow-up of 11.8 years, 80 IgAN-patients died, compared to 42 deaths expected from sex- and age- and time-period standardized census data, resulting in an SMR of 1.9. The main cause of death was vascular disease.[97] Mortality was not increased in patients with eGFR ≥ 60 mL/min/1.73m^2, proteinuria < 1 g/day or a 10-year risk of ESRD < 10 %, according to a clinical–histological risk stratification model.[98] When studying only the pre-ESRD period, SMR was reduced to 1.3 and not significantly increased, compared to an SMR of 4.9 during RRT, 10.3 in dialysis patients compared to 3.2 in transplant recipients.[97] None of these studies reported on reduction in life expectancy. In another study, Hastings et al examined patient and kidney survival among IgAN-patients in Kentucky, USA. Among 251 patients with a median follow-up of 19.3 years, 132 proceeded to ESRD and 97 died. The median age at death was 65.7 years, with a 10.1 years' reduction in life expectancy. As opposed to the Korean and Norwegian cohort, a great majority of deaths (83 %) occurred after progression to ESRD. Compared with those studies, the Kentucky cohort had a more advanced IgAN, with a majority of patients in CKD stage GIII or worse, as well as with hypertension or proteinuria ≥ 1 g/day at inclusion.

Ischemic heart disease

Ischemic heart disease (IHD) is defined as hypoxia in myocardial cells due to impaired blood supply through the coronary vessels, and is mainly caused by atherosclerosis. Acute myocardial infarction (MI) is the irreversible loss of myocardial cells due to hypoxia, secondary to decreased blood supply. Atherosclerosis of the coronary vessels is a leading cause of mortality and morbidity in Sweden, as in other western countries. According to the National Patient Register (NPR), the 2019 incidence of acute myocardial infarction was 325 per 100,000 py, corresponding to more around 23,000 cases and more than 5200 deaths. Although sex difference has declined in recent years, the rates are still almost double in men (432) than in women (218 per 100,000 py). Including other IHD than MI, the 2019 incidence was 536 per 100,000 py (738 in men, 336 in women). The incidence increases with advancing age, but despite increasing life expectancy, rates have been declining steadily the last 20 years, supposedly reflecting healthier living habits including decline in smoking, and improved healthcare for risk factors for atherosclerosis, such as diabetes, dyslipidemia and hypertension.[99, 100]

Patients with CKD are at an increased risk of developing atherosclerosis and IHD.[92, 101, 102] Although there are known associations between IgAN and IHD risk factors such as hypertension, proteinuria and hyperuricemia,[103] data on the relation between IHD and IgAN are limited. There is evidence of both increased arterial stiffness and RAAS activity,[104] and high levels of markers of systemic and vascular inflammation even in early IgAN. A Finnish study found high rates of IHD and cerebrovascular in a cohort of 221 IgAN patients; however, this study is limited by different definitions of outcome in patients and reference individuals.[105]

High arterial blood pressure is a key for the development of atherosclerosis, and the kidneys play an essential role in systemic blood pressure regulation, both by the direct effects on glomerular filtration and tubular reabsorption of sodium and water, and by neuroendocrine regulation of vascular tone. In the healthy kidney, high arterial blood pressure leads to increased renal perfusion pressure and higher glomerular filtration rate of sodium and water, restoring blood pressure to normal, mediated in part by negative feedback on the RAAS, decreasing angiotensin II dependent vasoconstriction of the glomerular afferent arteriole. Renal parenchymal damage leads to upregulation of renin secretion and further activation of the RAAS, catalyzing the conversion of angiotensin into its active form angiotensin II, which is a strong peripheral vasoconstrictor and stimulator of further increases in sodium reabsorption through increased aldosterone activity.[106]

Pregnancy outcomes

Pregnancy implies dramatic physiologic changes in the childbearing woman, with changes in among others blood circulation and immunology to adopt to the demands of the growing fetus. Intercurrent diseases may both interfere with the physiologic changes in the pregnant woman and affect the fetal development. Chronic kidney disease during pregnancy is associated with increased risk for both maternal and fetal adverse outcomes, including maternal hypertension, preeclampsia and maternal death, as well as fetal growth restriction, preterm birth and the need for neonatal intensive care. In women with CKD, pregnancy also implies a risk for deteriorating kidney function.[107-109]

IgA nephropathy has its peak incidence during the third and fourth decades of life, coinciding with reproductive age, and might be of great concern in affected women. Hypertension and proteinuria are common in IgAN, overlapping with the key features of preeclampsia, with poses threat to both

the mother and the fetus. However, earlier studies of IgAN in pregnancy focus on "what pregnancy does to IgAN", where pregnancy is the exposure and kidney function or proteinuria is the outcome. In one systematic review, women with IgAN with predominantly well-preserved kidney function before conception were not at increased risk for adverse renal outcomes.[110] Few studies address pregnancy outcomes with IgAN as the exposure. Recent systematic reviews and meta-analyses suggest that women with IgAN may be at increased risk of preeclampsia, preterm birth and low birth weight.[111, 112] However, earlier studies either lack a matched pregnant reference group of pregnant women without IgAN,[110, 111, 113-116] or study IgAN as part of a mixed exposure of different glomerular diseases, with IgAN constituting only a minority.[109, 117, 118]

Register studies

Sweden has a long tradition of epidemiologic research based on national registers of high data quality and with excellent coverage. As data are identifiable to the individual level by a unique personal identification number (PIN), linkage between different registers is possible.[119, 120]

Database validation

National health and population registers constitute a tremendous source of information for epidemiological research, allowing researchers to combine data sources to identify both exposure and outcome in relation to the research question. However, every chain is only as strong as its weakest link. In quantitative research, an analysis is never stronger than the quality of the data entered. This applies largely to register studies, where the researcher takes advantage of information that might originally have been collected for various purposes, and has no or limited opportunities to govern data collection. Data on diagnoses or other relevant measures may be missing, unspecific or wrongly coded. Hence, how do we know that we measure what we set out to measure? The key is data validation, using structured methods to ascertain data quality. If done with an external data source, the validation preferably should result in a positive predictive value (PPV) for the corresponding diagnoses being calculated, i.e. the proportion of individuals that truly have the condition of interest among all individuals that are assigned the same condition in the database, and sensitivity, i.e. the proportion of patients with the condition of interest identified by the register. Under certain conditions, the validation procedure could also determine a negative predictive value (NPV), i.e. the proportion of individuals truly lacking the

condition of interest among all who are not assigned this condition in the database.[121]

There have been several efforts made to validate the data quality in several Swedish registers. The Swedish National Patient Register (NPR) is kept by the National Board of Health and Welfare (NBHW, Socialstyrelsen) and contains hospital discharge data from 1964 onwards, with national coverage since 1987. Outpatient visits in public hospitals (but not in private hospitals or primary health care) are included since 2001. Reporting to the register is mandatory. The NPR contains information on caregiver, dates of admission and discharge of somatic and psychiatric care, as well as main and additional diagnosis and surgical procedures, with the corresponding International Classification of Diseases (ICD) codes and procedure codes. Patients are listed by their unique 10-digit personal identity number (PIN), enabling for linking to other registers. Coverage is calculated by the NBHW, and a main diagnosis was registered for 98.9 % of hospital stays and for 97.1 % of outpatient visits in 2020.[122] A review of 132 articles validating various diagnoses in the NPR was published in 2011. The majority of validations was performed by manual review of patient charts to determine PPV. Various external sources were used to assess sensitivity. PPV was 85-95 % for most diagnoses. Sensitivity was generally higher for more severe diagnoses, e.g. > 90 % for myocardial infarction (MI) or stroke, but much lower for less severe conditions mainly cared for in an outpatient setting, e.g. hypertension, hyperlipidemia or asthma.[123]

As there is no specific ICD code for IgAN, the NPR is not suitable for identifying IgAN patients. Defining IgAN by the recommended ICD-10 code N03.3 "Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis" would not be specific enough, as this code refers to other mesangial proliferative GN:s as well, including class II lupus nephritis. On the other hand, some IgAN patients might be hidden by e.g. the code N03.9 "Chronic nephritic syndrome with unspecified morphologic changes" or some N05 codes, and N03.3 might then also not be sensitive enough. Therefore, a specific IgAN database was created based on pathology reports.[124] To ascertain this database contained true IgAN cases and to characterize our cohort, we performed a diagnosis validation study by manual patient chart review for a subset of patients.

Aims of the thesis

- To validate the diagnosis of IgAN in Swedish biopsy registers against patient charts.

- To describe the clinical characteristics of a cohort with patients with a biopsy indicating IgAN.

- To examine absolute and relative all cause and disease specific mortality in IgAN, compared with matched reference populations, before and after the progression to end-stage renal disease.

- To examine absolute and relative risks for IHD in patients with IgAN.

- To evaluate the risk of adverse pregnancy outcomes for mother and child in women with IgAN diagnosed before pregnancy.

Subjects and methods

While the studies in my thesis were all retrospective, studies II-IV exploited prospectively collected data taking advantage of the Swedish national health care and population registers, and the possibility to link register data through the unique 10-digit personal identity number assigned to all Swedish residents.

Registers

The four studies of this thesis all rely on the existence of Swedish national registers with high coverage and good data quality.

The personal identity number (personnummer)

The Swedish personal identity number (PIN) is a unique number assigned to every individual who resides in Sweden on a permanent basis. The number was introduced in 1947 and originally consisted of a six-digit birth date and a three-digit birth number, with the last digit assigned according to sex (odd for males, even for females). In 1967, a fourth check digit was added to the birth number, verifying the first 9 digits by the modulus-10 method. The PIN is assigned to every Swedish citizen at birth (within one month of birth according to law). Immigrants who intend to stay for at least one year will also be assigned a PIN. A PIN assigned to an individual may not be exchanged except for very special reasons, such as initially wrongly assigned birth date in immigrants, change of juridical gender or high-level protected identity. Until January 2008, less than 1 % of the individuals registered in Sweden had received a new PIN.[120] The PIN is used in all contacts with health care and authorities. It is also the unique identifier in national census and health care registers and as such enables cross-linkage of different registers for the purpose of epidemiological research.

The Total Population Register (Register över totalbefolkningen) and the Multi-generation Register (Flergenerationsregistret).

Sweden has a long tradition of registering its citizens. Local parish registers have been kept sins the 17th century and a national population statistics have been kept since the mid-18th century. Major reformations of the registration procedures were performed between 1947 and 1967 including the assignment of a PIN as a unique identifier of each individual and computerization. In 1991, the responsibility for Total Population Register (TPR) was transferred to the Swedish Tax Agency. The TPR contains information on all

Swedish residents, including PIN, name and sex, civil status, divorce and marriage, living address, level of education, date and place of birth, date and county of death, date and country of immigration, emigration and citizenship. The Multi-generation register (MGR) is part of the TPR, linking all (biological and adopted) first-degree relatives to every person in the register born since 1932 and who was still alive in 1961. The TPR is updated monthly. Data quality is generally very high. Reports of births and deaths within 30 days almost 100 %, the corresponding rates for immigrations and emigrations are 95 % and 91 %.[125]

For the studies of my thesis, TPR data are used to identify matched reference populations, dates of birth, death and emigration, level of education and first-degree relatives.

The National Patient Register (Patientregistret)

The Swedish National Patient Register (NPR) was first issued in 1964 by the National Board of Health and Welfare (NBHW; Swedish Socialstyrelsen) as the National Inpatient Register (IPR, also called the Hospital Discharge Register, (Slutenvårdsregistret)). The NPR has national coverage of psychiatric and somatic inpatient care from 1987 onwards, enhanced by an extensive backwards registration that took place in the early 1990s. From 1997 onwards, the NPR also contains data on community-based hospital outpatient visits. Coverage is virtually 100 % for inpatient care and approximately 80 % for hospital outpatient care, as data from private caregivers are lacking. Primary health care is not covered by the NPR.[123]

The NPR uses the PIN as unique identifier, and contains information on primary and secondary diagnoses with the corresponding International Classification of Diseases (ICD) codes (starting with ICD-7, currently ICD-10), external causes of injury end disease, and surgical and medical procedures, from 1997 onwards according to the NOMESCO standard (In Swedish KVÅ; 1964-1996 an American 4-digit standard was used). The NPR also contains data on sex, age, county of residence, hospital and type of department, dates and modes of admission and discharge (alive or deceased, from and to home or other institution) and length of stay.[123]

The NPR has been validated for several diagnoses, PPVs for most conditions lie between 85 % and 95 %, with generally higher accuracy for more severe conditions.

For studies II and IV of my thesis, the NPR was used to define outcomes. For studies II-IV, the NPR was used to define medical conditions entered as

covariates in the statistical models, and to identify a subclass of IgAN patients with systemic IgAV (Henoch's-Schönlein's purpura).

The Cause of Death Register (Dödsorsaksregistret)

The registration of death causes in Sweden dates back to the mid-18th century. As the registration was transferred to Statistics Sweden (Statistiska Centralbyrån, SCB) in 1911, the Cause of Death Register (CDR) was expanded from certain "important" causes to cover all causes of death. The CDR was computerized in the 1960s, and due to retrospective compilation, coverage is close to 100 % from 1952 onwards. Reporting to the CDR is mandatory for physicians in Sweden. The physician confirming the death immediately issues a "death notification" (dödsbevis) to the Swedish Tax Agency. A medical death certificate (dösdorsaksintyg) containing the cause of death then must be issued to the NBWH within three weeks, usually either by the physician confirming the death or by the patient's attending physician. The death certificate specifies the underlying causes of death, as well as contributory causes, following the International Form of Medical Certificate of Cause of Death.[126]

The CDR uses the PIN as unique identifier, and contains background data on PIN, sex, nationality, date and country of birth, marital status and place of residence. Data concerning the death includes date and place of death, autopsy, death abroad or within 4 weeks after surgery, and underlying and contributory causes of death based on ICD codes. Entering ICD codes is not mandatory for the reporting physician, and is completed by the registrar at NBWH according to the World Health Organization (WHO) standard. In the case of a missing or incomplete death certificate, the NBHW contacts the caregiver for completion, and an underlying cause of death is missing in less than 1 % of the posts.[126]

In study II the CDR was used to study cause-specific mortality, and in study III to complete data from the NPR in the definition of the outcomes (ischemic heart disease and myocardial infarction).

The Prescribed Drug Register (Läkemedelsregistret)

The Swedish Prescribed Drug Register (PDR) was established in July 2005. The register has national coverage and holds information on all prescribed drugs dispensed from Swedish pharmacies in ambulatory care, with the PIN as unique patient identifier. Drugs delivered in hospitals and over-the-counter medicines are not included. The PDR contains data on the patient (PIN, age, sex and place of residence), the prescriber (profession, field of practice,

and the practice identified by a unique code) and the prescription (substance, anatomical therapeutical chemical (ATC-) code, brand name, formulation and package as well as date, prescribed amount, dosage, expenditure and reimbursement according to the law of pharmaceutical benefits).[127] The indication for prescription is not included in the PDR. Therefore, it could not be concluded from the register for example whether doxycycline was prescribed for acne or Lyme borreliosis, and a prescription of losartan could be intended for proteinuria reduction as well as for hypertension or chronic heart failure.

In study II of my thesis, data from the PDR were used to study mortality in relation to drugs commonly used in IgAN patients. For study III, we used the PDR data to study hypertension

The Medical Birth Register (Medicinska födelseregistret)

The Swedish Medical Birth Register (MBR) contains information on maternal demographic data, reproductive history, and pregnancy outcome and complications. Data are collected prospectively from the first antenatal visit, usually before 12 weeks gestational age, through delivery and the immediate postnatal period. The register was established in 1973. Data in the MBR have been validated in 1976 based on 1974 data, in 1988 based on 1986 data and in 2001 based on 1998 data against census data and through comparisons to a selection of original patient records. More than 98 % all births are covered.

We used MBR data for to define both outcomes and covariates in study 3 of this thesis. To enable adjustment for body mass index (BMI) and smoking habits, we enrolled only pregnancies from 1992 onwards, as these data were not consistently reported earlier.[128]

The IgAN cohort

As a renal biopsy with the demonstration of IgA in the renal mesangium is required for IgAN diagnosis, we could use pathology reports to define our IgAN cohort, used in studies I-IV, as described in detail by Welander et al.[124] In Sweden, the evaluation of renal biopsies is centralized to the four pathology laboratories in the university hospitals in Gothenburg, Linköping, Malmö/Lund and Stockholm. Computerized pathology reports have been used in Sweden since the early 1990s, with extensive backwards registration. In most departments, these reports are coded according to the Systematized Nomenclature of Medicine – Clinical Term (SNOMED CT). This is a multilingual system with hierarchical structure defining disease processes

and other medical entities, using terms for location, disease process and causative agent. Local lab technicians performed computerized searches of the SNOMED code for IgAN (67300) and location in the kidney (T71000). The Malmö/Lund lab did not provide SNOMED codes, mandating manual screening of pathology reports from this department. IgAN in this case was defined by reports where the pathologist both described findings consistent with IgAN and stated IgAN as the primary diagnosis. This screening identified 4126 patients with a pathology report indicating IgAN.

Reference individuals

Primary comparison group

For each individual in the IgAN cohort, Statistics Sweden selected up to five reference individuals (general population controls) without IgAN (i.e. that were not included in the IgAN cohort described above) from the TPR, matched to the corresponding IgAN patient at the time of biopsy by sex, birth year, county of residence and calendar year.

Secondary comparison groups

Despite matching and statistical adjustment for possible confounding factors, there might be residual confounding due to differences between IgAN patients and reference individuals that influence the outcome variables, but that are not caused by IgAN. A possible way around this is to use secondary comparison groups that could be expected to share risk factors with the IgAN patients. We included two such comparison groups for sensitivity analysis: siblings and spouses. Through the TPR, Statistics Sweden identified all siblings and the first spouse of each IgAN patient. Siblings and spouses that with IgAN or who had died before the date of renal biopsy were excluded.

Selection of individuals for the final analyses

From the cohort of 4126 IgAN patients, further inclusion and exclusion procedures were performed for the separate studies.

- In study I, we randomly selected a subset of patients were randomly selected from the cohort of 4126 patients with renal biopsy reports suggesting IgAN, that had been identified through screening of renal biopsy data. EpiTools (epitools.ausvet.com.au) was used for sample size calculation and we estimated that we needed

to examine 139 patient files to detect a positive predictive value (PPV) of 90 % with a 95 % confidence interval (CI) of 85 % - 95 %. As we could not expect to receive all charts, we requested a total of 150 patients were selected for patient chart evaluation.

- In study II, end-stage renal disease (ESRD) was one of the outcome measures. Hence, patients with ESRD before study entry were excluded. ESRD was defined as having an ICD code of CKD stage 5, renal transplantation or chronic dialysis, either in the NPR or as underlying or contributory cause of death in the CDR.
- In study III, the first occasion of ischemic heart disease (IHD) was studied as the outcome. Therefore, patients with IHD before study entry were excluded, defined by the corresponding ICD codes in the NPR. To increase specificity, a dialysis code must be repeated at least three times during a minimum period of four months.
- In study IV, we used a somewhat different inclusion procedure. From the complete database of IgAN patients, population controls and siblings, all female individuals with at least one pregnancy registered in the MBR after renal biopsy date were included. We then excluded all pregnancies before January 1, 1992, and in a second step IgAN patients without pregnant controls, and control subjects without a pregnant IgAN patient. Each woman could contribute with more than one pregnancy.

Design and statistical analyses of the studies

Study I: database validation and IgAN cohort description

In a descriptive observational study, complete patient charts including paper and electronic records as well as lab results were requested for a random selection of 150 individuals from 43 clinical units in 32 hospitals that had referred the patients for renal biopsy. Patient charts were reviewed according to a standardized template, including demographic data (age, sex, county), cause of consultation, date of renal biopsy and last follow up, clinical and laboratory data at time of biopsy including macro- or microscopic hematuria, grade of proteinuria, smoking habits, comorbidities and prior use of antihypertensive drugs. We also noted family history of IgAN, other kidney disease or ESRD. The biopsy reports were reviewed and the presence

of mesangial hypercellularity, fibrosis and crescent formation, as well as immunofluorescence staining of and IgA, IgG, C3 and C1q. In particular, we noted any indications in the patient charts or biopsy reports that the patient may not have IgAN. Based on these data, the patients were classified as IgAN ruled out or unlikely, IgAN probable or IgAN confirmed. Ambiguous cases were discussed within the research group and settled by consensus.

Using confirmed or probable IgAN according to the patient chart review as gold standard, a PPV of a biopsy report indicating IgAN was calculated with 95 % CI.

Study II: mortality

In a population-based cohort study, all-cause and cause-specific mortality was studied in IgAN patients compared with matched controls, as well as with their siblings and spouses. Data on death date was extracted from the TPR and death cause from the CDR. Follow-up started at the date of renal biopsy and ended at death (and the corresponding date in controls), emigration or May 31, 2017, whichever occurred first. We also studied mortality separately in IgAN patients before and after the progression to ESRD, and mortality in relation to medication (data from the PDR).

Survival analysis was performed with Cox regression with internal stratification (each IgAN patient is compared with his or her own matched controls, spouse or siblings), and results were presented with survival curves and hazard ratios (HR) with 95 % CIs, with adjustment for educational level, heredity for IgAN, heredity for ESRD, and the presence at baseline of any cardiovascular disease, cancer (except basalioma), diabetes, and any other systemic inflammatory disease. As sibling and spousal comparisons were unmatched for sex and age, these variables were instead adjusted for in the model. Hazard ratios were also calculated for a variety of strata defined by among others inclusion date, age at inclusion, length of follow-up and comorbidities and separately for the first year of follow-up. In a post-hoc sensitivity analysis, we also calculated unadjusted HR and HR adjusted for all confounders except cardiovascular disease. We also calculated unadjusted absolute risk differences.

Study III: Ischemic heart disease

In a population-based cohort study, we examined incident ischemic heart disease (IHD) in IgAN patients compared with matched controls from the general population, with secondary comparisons with siblings and spouses. The primary endpoint was the first occasion of fatal or non-fatal IHD, based

on the corresponding ICD codes for myocardial infarction and stable or unstable angina pectoris in the CDR and the NPR. In a secondary analysis, the endpoint was restricted to myocardial infarction. Follow-up began at the day of renal biopsy in the IgAN patients and the corresponding date in primary and secondary controls, and ended by IHD, death, emigration or May 31, 2017, whichever occurred first.

We performed survival analyses by Cox regression with internal stratification, and presented the results as survival curves and adjusted HR with 95 % CIs. HRs were calculated in separate strata based on background variables and length of follow-up. Unadjusted absolute risk differences were also presented.

Study IV: Pregnancy

In a population-based cohort study, we studied maternal and infant pregnancy outcomes in women with IgAN (diagnosed before pregnancy), compared with a matched reference population without IgAN. The main outcome was preterm birth before the end of the 37th gestational week. Secondary outcomes included preeclampsia, being born small for gestational age (SGA), cesarean section, stillbirth or neonatal death, neonatal distress (defined by Apgar score < 7), and gestational diabetes (GDM), and the progression to ESRD. Outcome data were extracted from the MBR, for GDM and preeclampsia also from the NPR. Follow-up started at pregnancy start and ended by the end of pregnancy.

Data were analyzed through multivariate logistic regression with cluster robust standard errors. For power reasons, matching was broken. The models were adjusted for age, calendar year of conception, parity, multiple gestation, educational level, body mass index (BMI), smoking status and the presence before pregnancy start of diabetes, hypertension or chronic inflammatory diseases.

Data were presented as frequencies and as adjusted odds ratios (ORs) with 95 % CIs.

Statistical analysis

Cox regression (study I and II)

For group comparisons through survival analysis, we used Cox proportional hazards regression with internal stratification to estimate hazard ratios (HRs). Internal stratification means that each IgAN patient was compared only to his or her own matched controls in the primary analyses and

to his or her siblings or spouse in the secondary analyses. Results were presented by either unadjusted (Kaplan-Meier) or Cox adjusted survival curves.

Logistic regression (study III)

We compared women with IgAN with pregnant reference individuals from m the general population. To increase statistical power, matching of each IgAN patient to her reference was omitted, and any difference in time period was handled by statistical adjustment. We analyzed all outcomes as dichotomous variables (yes/no). Groups were compared by logistic regression with cluster-robust standard errors to calculate odds ratios (OR), adjusted for year of conception, maternal age, BMI, educational level, smoking status, pre-pregnancy diabetes (except in the analysis of gestational diabetes), other autoimmune diseases, and multiple gestation pregnancies. Fetal outcomes (except stillbirth) were analyzed by child. Maternal outcomes and stillbirth were analyzed by pregnancy. Follow-up started at pregnancy start and ended at delivery, for neonatal mortality 28 days after birth.

Ethical considerations

All studies included in this thesis were performed in accordance with the ethical standards of the Helsinki declaration, and approved by the Stockholm Ethics Review Board; study 1 in March 31, 2010 (dnr 2010/407-31/1) and studies II-IV in January 22, 2014 (dnr 2013/2095-31/2). Informed consent was deemed unnecessary by the board. Since there were no interventions, the main ethical concern is about the research participants' personal integrity. The high data quality and wide coverage of Swedish health care and population registers make an excellent base for epidemiologic research. On the other side, the broad collection of data might imply risks for the personal integrity if not wisely handled.[119]

In study 1, IgAN biopsy data and patient files were manually screened by one researcher and treated confidentially with open patient data. During data processing, these were kept in an encrypted and password protected file in a password protected computer. A backup file was stored in a locked space in the researcher's clinical department. After compilation, a copy of the patient files are securely stored for ten years in the hospital archive. Whenever cases were discussed within the research group, name ad PIN of the patients ware substituted by serial numbers.

For studies II-IV, the crosslinking of IgAN biopsy data with national registers was performed at the NBHW and Statistics Sweden. In the datasets

delivered to the researchers, the PIN of each research participant was exchanged for a unique serial number, and no name or other data traceable to a specific individual was available for the researchers. A code key was stored at the NBHW for three years.

In study I, we mistakenly reported the wrong ethical decision number. The correct number has been uploaded in a corrigendum published in 2022.[129]

Results

Study I

Validation of IgAN diagnosis from renal biopsy reports.

Out of the intended 150 patient files, we retrieved 127 files for evaluation. Two units did not provide patient charts for ten patients, including six children. For another thirteen patients, patient charts were incomplete or could not be located. Immunoglobulin A nephropathy was confirmed in 116 patients and likely in on another five patients. Hence, the positive predictive value of a biopsy report diagnosis of IgAN was 95 % (95 % CI = 92-99 %).

IgA deposits were present in 123 patients. In three patients were IgAN was deemed likely, the biopsy showed predominantly chronic changes and IgAN was stated as "probable" both by the pathologist and the clinician. In one patient with macroscopic hematuria following a throat infection, the biopsy showed mesangial proliferative glomerulonephritis suggestive of IgAN, but the diagnosis could not be confirmed due to failed immunofluorescence staining. For the fifth patient, IgAN deposits were mainly of capillary location and even though IgAN was stated as a probable diagnosis by the clinician, the patient charts available were incomplete. In three patients with no mention of IgAN deposits in the biopsy report, IgAN was ruled out due to other renal diagnoses (systemic lupus erythematosus (SLE) or nephropathia epidemica due to Puumala virus). In three patients with IgAN deposits, the picture was better explained by some other disease (Goodpasture's disease, steroid responsive nephrotic syndrome due to minimal change nephropathy and toxic nephropathy due to ethylene glycol poisoning), and IgAN was considered unlikely. Age and sex distribution of the 116 patients with confirmed IgAN did not differ from all the 127 patients whose charts were evaluated. The 23 patients with unavailable charts were biopsied ten years earlier and were younger (26 % were < 16 years) at the time of biopsy.

IgAN patient characteristics

Patient characteristics are summarized in table 3. Among the patients whose IgAN diagnosis was confirmed or likely, 74 % were male, the mean age was 39.6 years and 6 % were < 16 years at the time of biopsy. The most common cause of consultation was macroscopic (29 %) hematuria, in most cases (21 %) following an infection, followed by screening in patients with

hypertension or microscopic hematuria (26 %) and purpura (11 %). Fourteen percent of the patients had extra-renal manifestations compatible with systemic IgAV and 46 % had confirmed hypertension.

Cause of consultation:	***n* (%)**
Infection-related macroscopic hematuria	27 (21)
Macroscopic hematuria (without mention of infection)	10 (8)
Purpura	14 (11)
Malignant hypertension	5 (4)
Nephrotic syndrome	4 (3)
Renal failure	5 (4)
Screening (including hypertension or microscopic hematuria)	33 (26)
Joint pain	3 (2)
Flank pain	8 (6)
Other or unknown	12 (10)
Family history:	***n* (%)**
Family history of renal disease	20 (16)
Family history of ESRD	9 (7)
Family history of IgAN	8 (6)
Lab and clinical data (*n* = patients with available data)	
Creatinine (µmol/l; *n* = 110; median (range)	104 (26-986)
GFR (ml/min/1,73m^2; *n* = 114; median (range)	75 (5-173)
CKD 1-2 GFR ≥60 (*n*; %)	75 (59)
CKD 3 GFR ≥30 and <60 (*n*; %)	20 (16)
CKD 4 GFR <30 (*n*; %)	21 (17)
Systolic BP (mmHg; *n* = 102; mean ±SD)	138 ±22
Diastolic BP (mmHg; *n* = 102; mean ±SD)	83 ±15
Hypertension (BP >140/80 mmHg or on antihypertensive treatment (*n*; %)	59 (46)
Antinuclear antibodies (*n* = 68), (*n*; %)	6 (5)
Viral hepatitis (*n* = 51), (*n*; %)	3 (2)
Anti-neutrophilic cytoplasmic antibodies (ANCA) (*n*; %)	5 (4)
Microscopic or macroscopic hematuria (*n* = 119)	116 (91 %)
Significant proteinuria (dU-albumin > 1g/24h, dU-protein >1,5 g/24h, U-albumin >1 g/L or U-ACR >100 g/mol (*n* = 98)	56 (44 %)

Table 3. Characteristics of patients with confirmed or likely IgAN.

Biopsy findings are shown in table 4. In a vast majority of the biopsies, IgAN was found in at least moderate abundance and with moderate or strong immunofluorescence.

	All individuals	Confirmed IgAN
n	127	116
IgA deposits: moderate or rich amount *or* moderate or strong fluorescence, *n* (%)	107 (84)	105 (91)
Mesangial hypercellularity, *n* (%)	96 (76)	92 (79)
C3 deposits, *n* (%)	113 (89)	104 (90)
C1q deposits, *n* (%)	15 (12)	14 (12)

Table 4. Biopsy findings in patients with a biopsy diagnosis of IgAN.

Study II

Baseline characteristics and demographic data

From our main cohort of 4126 IgAN patients, we excluded 504 (12.2 %), mainly because of ESRD diagnosis before IgAN biopsy date (n = 503; one because of redundant PIN). Hence, we included 3622 patients in the main analysis, of which 227 (6.3 %) had also extra-renal IgAV/HSP. The IgAN patients were matched to 18,041 general population controls. For the secondary analyses, we included 2773 IgAN patients with 6210 siblings and 2234 couples for the spousal comparison.

Demographic and other background data are displayed in table 5. The median age at biopsy was 34.9 years, with 10 % biopsied in childhood and 14 % at 60 years or older. The male to female ratio was 7:3. The median time of follow-up was 13.6 years for IgAN patients and 14.1 years for controls; 3207 (89 %) of the patients were followed for more than 5 years, 994 (27 %) for more than 20 years and 234 (6 %) for more than 30 years. As a result of matching, demographic variables were similar in IgAN patients and general population controls, except for patients less often being of non-Nordic origin. IgAN patients had more often diabetes or some other systemic inflammatory disease and much more cardiovascular comorbidity (including hypertension).

	IgAN	Controls	IgAN	Siblings	IgAN	Spouses
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	3622	18041	2773	6210	2234	2234
Matched variables						
Sex						
Female	1084 (30 %)	5408 (30 %)	802 (29 %)	3036 (49 %)	664 (30 %)	1591 (71 %)
Male	2538 (70 %)	12633 (70 %)	1971 (71 %)	3174 (51 %)	1570 (70 %)	643 (29 %)
Age						
Age, median (IQR)	38.8 (26-52)	38.7 (26-52)	34.9 (23-47)	35.8 (23-48)	43.7 (33-55)	43.3 (32-54)
≤17 years	370 (10 %)	1843 (10 %)	351 (13 %)	1025 (17 %)	62 (2.8 %)	90 (4.0 %)
18-39 years	1548 (43 %)	7754 (43 %)	1346 (49 %)	2601 (42 %)	864 (39 %)	864 (39 %)
40-59 years	1214 (34 %)	6010 (33 %)	887 (32 %)	2115 (34 %)	949 (42 %)	949 (42 %)
≥60 years	490 (14 %)	2434 (13 %)	189 (6.8 %)	469 (7.6 %)	359 (16 %)	326 (15 %)
Unknown					0 (0.0 %)	5 (0.2 %)
Calendar year of inclusion (date of renal biopsy in IgAN patients)						
1974-1988	428 (12 %)	2135 (12 %)	311 (11 %)	712 (11 %)	317 (14 %)	317 (14 %)
1989-2001	1448 (40 %)	7214 (40 %)	1086 (39 %)	2447 (39 %)	974 (44 %)	974 (44 %)
2002-2015	1746 (48 %)	8692 (48 %)	1376 (50 %)	3051 (49 %)	943 (42 %)	943 (42 %)
Un-matched variables						
Follow-up time						
Median (IQR)	13.6 (7.99-20.8)	14.1 (8.32-21.5)	14.3 (8.46-21.4)	14.8 (9.01-22.2)	15.3 (8.93-22.4)	16.0 (9.57-23.3)
<1 years	49 (1.4 %)	152 (0.8 %)	15 (0.5 %)	30 (0.5 %)	29 (1.3 %)	15 (0.7 %)
1-4 years	366 (10 %)	1690 (9.4 %)	238 (8.6 %)	469 (7.6 %)	197 (8.8 %)	147 (6.6 %)
≥5 years	3207 (89 %)	16199 (90 %)	2520 (91 %)	5711 (92 %)	2008 (90 %)	2072 (93 %)
Reason for ending the follow-up						
Death	577 (16 %)	2066 (11 %)	257 (9.3 %)	362 (5.8 %)	400 (18 %)	245 (11 %)
Emigration	101 (2.8 %)	664 (3.7 %)	76 (2.7 %)	152 (2.4 %)	47 (2.1 %)	39 (1.7 %)
May 31, 2017	2944 (81 %)	15311 (85 %)	2440 (88 %)	5696 (92 %)	1787 (80 %)	1950 (87 %)
Person-years	54058	277463	43106	99467	35774	37566

	IgAN	Controls	IgAN	Siblings	IgAN	Spouses
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Country of origin						
Nordic	3317 (92 %)	16277 (90 %)	2715 (98 %)	6069 (98 %)	2008 (90 %)	1963 (88 %)
Non-Nordic	304 (8.4 %)	1762 (9.8 %)	58 (2.1 %)	141 (2.3 %)	226 (10 %)	211 (9.4 %)
Unknown	1 (<1 %)	2 (<1 %)			0 (0.0 %)	60 (2.7 %)
Educational level						
Compulsory school, ≤9 years	770 (21 %)	3823 (21 %)	468 (17 %)	1140 (18 %)	518 (23 %)	435 (19 %)
Upper secondary school, 1-3 yrs	1611 (44 %)	8016 (44 %)	1300 (47 %)	2941 (47 %)	955 (43 %)	984 (44 %)
University level	1148 (32 %)	5745 (32 %)	958 (35 %)	1908 (31 %)	734 (33 %)	732 (33 %)
Unknown	93 (2.6 %)	457 (2.5 %)	47 (1.7 %)	221 (3.6 %)	27 (1.2 %)	83 (3.7 %)
IgAV (Henoch-Schönlein purpura)[a]						
Yes	227 (6.3 %)	26 (0.1 %)	191 (6.9 %)	18 (0.3 %)	93 (4.2 %)	4 (0.2 %)
Medical history[b]						
Cardiovascular disease	1283 (35 %)	1595 (8.8 %)	867 (31 %)	455 (7.3 %)	863 (39 %)	252 (11 %)
Cancer	226 (6.2 %)	973 (5.4 %)	150 (5.4 %)	339 (5.5 %)	148 (6.6 %)	141 (6.3 %)
Diabetes, type 1 or 2	157 (4.3 %)	344 (1.9 %)	87 (3.1 %)	108 (1.7 %)	100 (4.5 %)	59 (2.6 %)
Other systemic inflammatory disease	292 (8.1 %)	434 (2.4 %)	205 (7.4 %)	198 (3.2 %)	189 (8.5 %)	74 (3.3 %)
First-degree relative with renal disease						
IgAN[c]	35 (1.0 %)	31 (0.2 %)				
ESRD	74 (2.0 %)	118 (0.7 %)				

Table 5. *Study II: Mortality in IgAN. Baseline characteristics and demographic data of IgAN patients and primary and secondary reference individuals. .*
[a] Within 1 year of first renal biopsy indicating IgAN. [b] Before study entry (date of biopsy and corresponding date in controls). [c] Same definition as in the IgAN cohort (biopsy report of IgAN 1974-2011).

Overall and cause-specific mortality

During a follow-up of 54,054 py, 577 (1.1 %) IgAN patients died (10.7 deaths per 1000 py), compared with 2066 deaths (0.7 %) in 277.463 py in the general population controls (7.4 per 1000 py). This corresponds to an unadjusted absolute excess mortality of 3.23 per 1000 py, or one extra death in 310 py. Median age at death was 77 years (95 % CI = 75.9-78.0) in the IgAN patients and 83 years (95 % CI = 82.4-83.5), indicating six years reduction in life expectancy. 10, 20 and 30 years survival rates were 91.3 % (95 % CI = 90.3-92.2 %), 80.7 % (95 % CI = 79.0-82.3 %) and 69.6 % (95 % CI = 66.7-72-3 %). Figure 2 shows Cox adjusted survival curves for mortality.

The fully adjusted death HR (aHR) was 1.53 (95 % CI = 1.37-1.72). Unadjusted HR was 1.83 (95 % CI = 1.65-2.02), and HR adjusted for all confounders except for cardiovascular disease was 1.74 (95 % CI = 1.57-1.94). Excess mortality was higher in the first year of follow-up (aHR 2.47; 95 % CI = 1.50-4.06). A tendency towards higher mortality in the earliest time period (1974-1988) was not statistically significant (p for interaction 0.21). Adjusted HRs were roughly similar in men and women and across all other strata (figure 3). Secondary comparisons with siblings and spouses resulted in generally similar HRs, with a few exceptions: women with IgAN had a lower death hazard compared with their predominantly male spouses. The higher aHR in the first year after biopsy was not seen in the sibling analysis.

The most common cause of death IgAN patients was 'other' (n = 214), followed by cardiovascular (n = 201) and cancer (n = 212). Death hazards from cardiovascular disease and (aHR 1.59; 95 % CI = 1.29-1.96) and from 'other causes' (aHR 1.58; 95 % CI = 1.58-2.32) was increased in IgAN patients compared with controls, but cancer death did not differ significantly (aHR 1.16; 95 % CI = 0.92-1.46).

For the period from 2005 onwards, mortality was not increased in IgAN patients who used RAASi (aHR 0.8; 95 % CI = 0.61-1.04) or statins (aHR 0.83; 95 % CI = 0.67-1.04) compared with matched controls.

In IgAN patients with ESRD (first renal replacement therapy as starting point and the corresponding date in controls), mortality was increased by an aHR of 3.14 (95 % CI = 2.61-3.78). On the contrary, mortality was not significantly increased in IgAN who had not reached ESRD (ESRD as censoring event; aHR 1.11; 95 % CI = 0.97-1.28).

Renal survival and ESRD

During a follow-up of 42,569 py, 803 IgAN patients (22.2 %) developed ESRD, compared with 67 (0.4%) during 255.365 py among controls, corresponding to an incidence per 1000 py of 18.86 in IgAN patients versus 0.26 in controls (aHR 100; 95 % CI = 67.7-148). ESRD-free survival rates at 10, 20 and 30 years of follow-up was 75.2 % (95 % CI = 73.6-76.7 %), 61.4 % (95 % CI = 59.3-63.4 %) and 50.7 % (95 % CI = 47.4-53.7 %) respectively (figure 2).

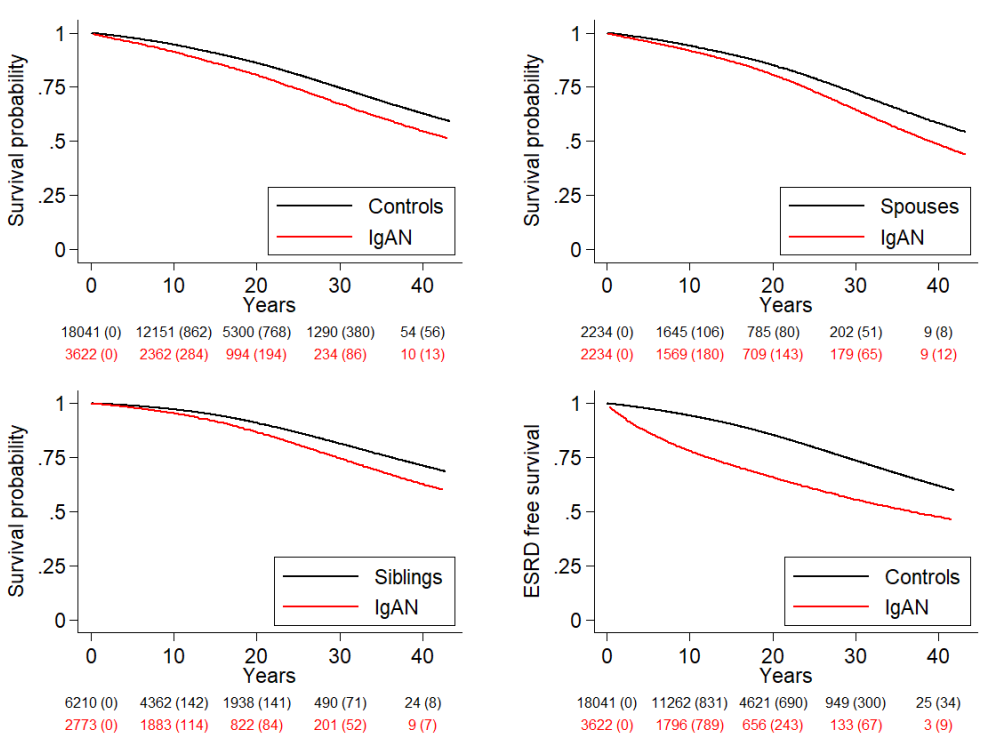

***Figure 2: Cox adjusted** survival curves. Survival of (upper left) IgAN patients vs their matched general population controls, (lower left) IgAN patients vs their siblings, (upper right) IgAN patients versus their (first) legal spouses. Lower right: ESRD survival of IgAN patients vs their matched general population controls.*

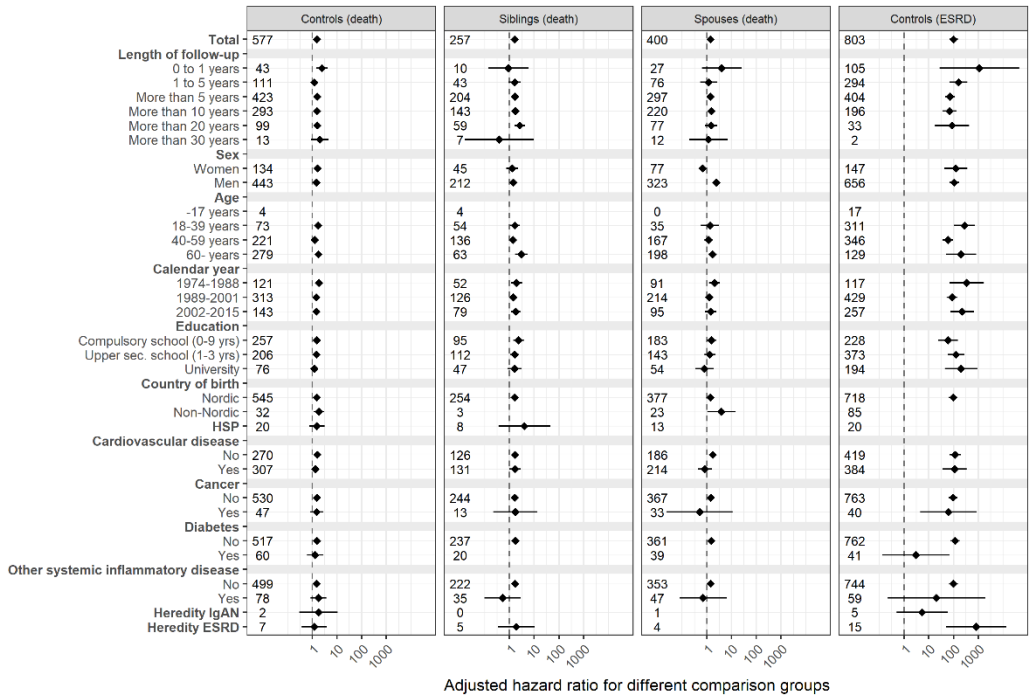

Figure 3. *Adjusted HRs for death and ESRD in patients with IgAN with subgroup stratification, showing increased mortality in IgAN compared with all reference groups, and increased ESRD compared with matched general population controls. Numbers represent absolute numbers of events in patients with IgAN. Whiskers represent 95 % CIs. HSP = Henoch-Schönlein's purpura (systemic IgAV).*

Study III

Baseline characteristics and demographic data

After exclusion from of 180 IgAN patients with IHD before inclusion date, 3945 patients remained for inclusion, with 19,272 individually matched general population controls. Baseline data are displayed in table 6. The male to female ratio was 7:3, and median age at inclusion was 38.9 years, with 380 patients (9.6 %) included during childhood (< 16 years). 236 IgAN patients (6 %) had extra-renal IgAV/HSP. In he the secondary analyses, 3039 IgAN patients were compared with their 6729 siblings and 2377 IgAN patients with their spouses.

The median follow-up time was 12.7 years in the IgAN patients versus 13.7 years in the controls. At study entry, 1241 (31.5 %) of the IgAN patients and 344 (1.8 %) among controls had a registered hypertension diagnosis, and 50.1 % of the IgAN patients had a hypertension diagnosis during follow-up. In 1343 IgAN patients included after July 1 2005 when we drug data are available, 1172 (87.3 %) received a prescription for a RAAS-inhibitor and 841 (62.3 %) for some other antihypertensive drug during follow-up. Statins were prescribed to 578 (43.0%) of patients. Systemic corticosteroids were prescribed to 784 (58.4 %) and other anti-inflammatory or anti-rheumatoid drugs to 345 (25.7 %) IgAN patients.

Main results: (any) ischemic heart disease

During a total follow-up of 55,527 py:s, 371 IgAN patients (9.4 %) had a first episode of IHD (6.7 per 1000 py). This compares to 1070 first IHD episodes during 287.677 py (5.6 %) in the general population controls (3.7 per 1000 py), with an absolute excess rate of 3.0 per 1000 py equal to one extra incident IHD per 337 py. Survival curves are displayed in figure 4.

The Cox regression aHR for IHD was 1.86 (95 % CI = 1.63-2.13). The excess IHD risk was higher in the first year of follow-up (aHR 2.63; 95 % CI = 1.57-4.41). Risk estimates were generally similar across strata (figure 5). Similar excess risks were seen in men (aHR 1.90; 95 % CI = 1.24-2.37) and women (aHR 1.72; 95 % CI = 1.24-2.37). There was a non-statistically significant tendency towards higher aHRs in IgAN patients diagnosed at a younger age, and in IgAN patients with lower education. Secondary analyses showed similar IHD excess rates compared with siblings (aHR 2.07; 95 % CI = 1.62-2.64) and spouses (aHR 1.91; 95 % CI = 1.40-2.61).

Myocardial infarction

During a total follow-up of 56,865 py 216 IgAN patients (5.5 %) had a myocardial infarction (MI), compared with MI observed in 662 controls (3.4 %) in 291.433 py in the controls. This equals to an unadjusted absolute excess rate of 1.5 per 1000 py or one incident MI in 650 py, with a corresponding aHR of 1.83 (95 % CI = 1.54-2.18).

	IgAN	Controls	IgAN	Siblings	IgAN	Spouses
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	3945	19272	3039	6729	2377	2377
Person-years	55527	287677	44796	105096	35484	38893
Matched variables						
Sex						
Female	1172 (30 %)	5780 (30 %)	869 (29 %)	3307 (49 %)	690 (29 %)	1710 (72 %)
Male	2773 (70 %)	13492 70 %)	2170 (71 %)	3422 (50 %)	1687 (71 %)	667 (28 %)
Age						
Age, median (IQR)	38.9 (27-51)	38.3 (26-51)	35.3 (24-47)	35.7 (23-48)	43.1 (33-54)	42.8 (32-53)
≤17 years	380 (9.6 %)	1894 (9.8 %)	361 (12 %)	1093 (16 %)	64 (2.7 %)	91 (3.8 %)
18-39 years	1706 (43 %)	8541 (44 %)	1485 (49 %)	2872 (43 %)	943 (40 %)	947 (40 %)
40-59 years	1390 (35 %)	6778 (35 %)	1015 (33 %)	2312 (34 %)	1046 (44 %)	1036 (44 %)
≥60 years	469 (12 %)	2059 (11 %)	178 (5.9 %)	452 (6.7 %)	324 (14 %)	296 (12 %)
Unknown					0 (0.0 %)	7 (0.3 %)
Calendar year of inclusion (date of renal biopsy in IgAN patients)						
1974-1988	438 (11 %)	2168 (11 %)	317 (10 %)	728 (11 %)	326 (14 %)	326 (14 %)
1989-2001	1565 (40 %)	7662 (40 %)	1187 (39 %)	2670 (40 %)	1024 (43 %)	1024 (43 %)
2002-2015	1942 (49 %)	9442 (49 %)	1535 (51 %)	3331 (50 %)	1027 (43 %)	1027 (43 %)
Un-matched variables						
Follow-up time						
Median (IQR)	12.7 (7.5-19.6)	13.7 (8.1-20.7)	13.5 (8.0-20.4)	14.5 (8.6-21.5)	13.8 (8.0-20.7)	15.5 (9.3-22.5)
0-1 years	79 (2.0 %)	194 (1.0 %)	35 (1.2 %)	41 (0.6 %)	56 (2.4 %)	20 (0.8 %)
1-4 years	464 (12 %)	2001 (10 %)	314 (10 %)	569 (8.5 %)	248 (10 %)	176 (7.4 %)
≥5 years	3402 (86 %)	17077 89 %)	2690 (89 %)	6119 (91 %)	2073 (87 %)	2181 (92 %)

	IgAN	Controls	IgAN	Siblings	IgAN	Spouses
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Reason for end of follow up						
May 31, 2017	3022 (77 %)	16000 83 %)	2524 (83 %)	6020 (89 %)	1759 (74 %)	2021 (85 %)
Emigration	105 (2.7 %)	727 (3.8 %)	80 (2.6 %)	160 (2.4 %)	48 (2.0 %)	45 (1.9 %)
IHD (death or diagnosis)	371 (9.4 %)	1070 (5.6 %)	206 (6.8 %)	242 (3.6 %)	290 (12 %)	126 (5.3 %)
Death from other cause	447 (11 %)	1475 (7.7 %)	229 (7.5 %)	307 (4.6 %)	280 (12 %)	185 (7.8 %)
Country of birth						
Nordic	3602 (91 %)	17322 90 %)	2971 (98 %)	6568 (98 %)	2128 (90 %)	2085 (88 %)
Non-Nordic	342 (8.7 %)	1948 (10 %)	68 (2.2 %)	161 (2.4 %)	249 (10 %)	229 (10 %)
Unknown	1 (<1 %)	2 (<1 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	63 (2.7 %)
Level of education						
Compulsory school (0-9 years)	817 (21 %)	3852 (20 %)	506 (17 %)	1195 (18 %)	527 (22 %)	435 (18 %)
Upper sec. school (10-12 years)	1759 (45 %)	8690 (45 %)	1415 (47 %)	3205 (48 %)	1007 (42 %)	1044 (44 %)
University (> 12 years)	1276 (32 %)	6279 (33 %)	1066 (35 %)	2090 (31 %)	816 (34 %)	817 (34 %)
Unknown	93 (2.4 %)	451 (2.3 %)	52 (1.7 %)	239 (3.6 %)	27 (1.1 %)	81 (3.4 %)
Comorbitity						
HSP/IgAV2	236 (6.0 %)	30 (0.2 %)	203 (6.7 %)	22 (0.3 %)	94 (4.0 %)	5 (0.2 %)
Diabetes, type 1 or 2	170 (4.3 %)	309 (1.6 %)	97 (3.2 %)	107 (1.6 %)	101 (4.2 %)	45 (1.9 %)
Other systemic inflammatory disease	313 (7.9 %)	459 (2.4 %)	224 (7.4 %)	207 (3.1 %)	193 (8.1 %)	77 (3.2 %)
Hypertension	1241 (31.5 %)	344 (1.8 %)	891 (29.3 %)	139 (2.1 %)	809 (34.0 %)	51 (2.1 %)
Heredity for IgAN	38 (1.0 %)	28 (0.1 %)				
Heredity for ESRD	84 (2.1 %)	139 (0.7 %)				

Table 6. *Study III: IgAN and IHD. Baseline characteristics and demographic data.*

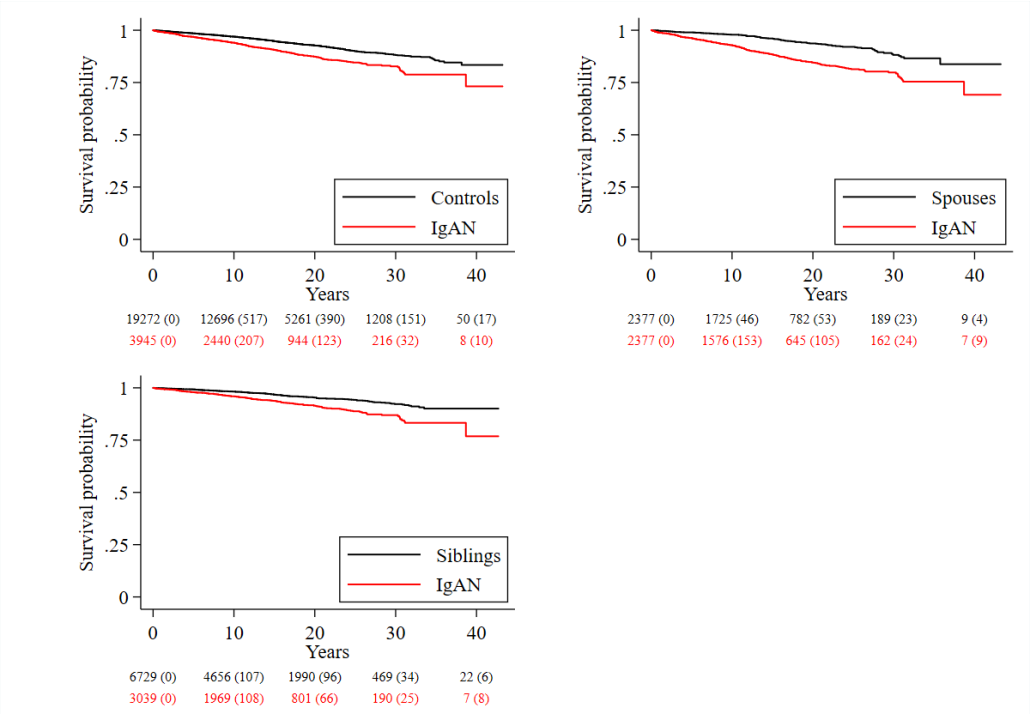

Figure 4. *Kaplan—Meier survival curves. IHD-free survival of (upper left) IgAN patients vs their matched general population controls, (lower left) IgAN patients vs their siblings, (upper right) IgAN patients versus their (first) legal spouses.*

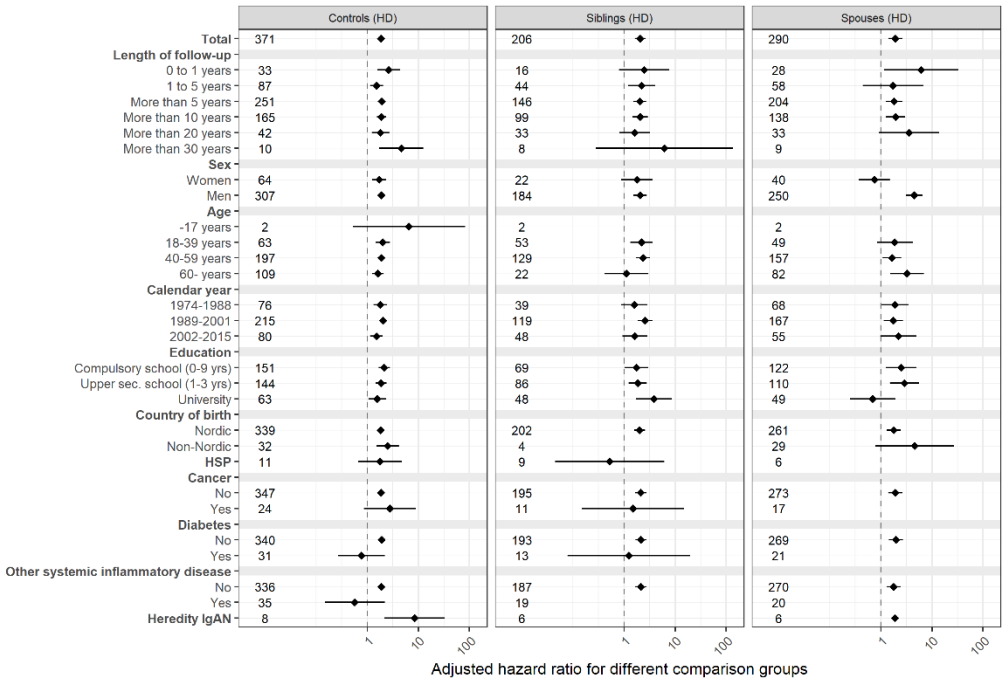

Figure 5. *Adjusted HRs for incident IHD in patients with IgAN with subgroup stratification, showing increased mortality in IgAN compared with all reference groups, Numbers represent absolute numbers of events in patients with IgAN. Whiskers represent 95 % CIs. HSP = Henoch-Schönlein's purpura (systemic IgAV).*

Study IV

Baseline characteristics and demographic data

We included 208 women with IgAN, giving birth to 333 children in 327 pregnancies to be compared with 622 control women without IgAN giving birth to 1088 children in 1060 pregnancies. In the secondary analysis we included 77 women with IgAN giving birth to 125 children in 122 pregnancies who were compared with their 90 sisters giving birth to 167 children in 160 pregnancies. Baseline characteristics are outlined in table 7. Diabetes before pregnancy was more frequent in IgAN patients compared with general population controls (OR 7.77; 95 % CI = 2.00-30.2), but not compared with their sisters (OR 1.07; 95 % CI = 0.28-4.07). Almost 9 % of IgAN women had a hypertension diagnosis before pregnancy, compared with 0.2 % in control women. Age, educational level, parity, BMI and smoking status was similar between groups.

Pregnancy-related outcomes

Pregnancy-related outcomes are displayed in table 8. Preterm birth before 37 gestational weeks was more common among women with IgAN (13.1 %) compared with controls (5.6 %; aOR 2.69; 95 % CI = 1.52-4.77). This increase was seen only for medically indicated preterm birth (induction of labor or non-acute cesarean section), not for spontaneous prematurity. Very preterm birth before 34 weeks' gestation was not significantly increased. IgAN was also associated with a higher rate of cesarean section. Preeclampsia was four times as common in women with IgAN, and their offspring were at increased risk of being born small for gestational age. Both stillbirth and neonatal death was uncommon in all groups and rates did not differ significantly between groups.

	Pregnancies IgAN women (n=333)	Control pregnancies (n=1088)	Pregnancies in IgAN women (n=125)	Pregnancies in sisters (n=167)
Calendar period of conception				
1992-1999	64 (19.2%)	183 (16.8%)	30 (24%)	28 (16.8%)
2000-2007	110 (33%)	379 (34.8%)	28 (22.4%)	54 (32.3%)
2008-2015	159 (47.7%)	526 (48.3%)	67 (53.6%)	85 (50.9%)
Age at conception				
median (IQR)	30 (27-33)	31 (28-34)	30 (28-33)	30 (26-34)
Educational level				
Compulsory	27 (8.1%)	64 (5.9%)	10 (8%)	4 (2.4%)
Upper sec.	137 (41.1%)	425 (39.1%)	51 (40.8%)	93 (55.7%)
College/univ.	167 (50.2%)	599 (55.1%)	64 (51.2%)	70 (41.9%)
Missing	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Parity				
Primiparous	126 (38 %)	445 (41 %)	47 (38 %)	68 (41 %)
Multiparous	207 (62%)	643 (59 %)	78 (62 %)	99 (59 %)
Body mass index (BMI, kg/m^2)				
median (IQR)	23.9 (22.0- 27.1)	23.7 (21.6-26.8)	23.3 (21.9-25.0)	23.6 (21.5- 26.9)
Smoking status				
Non-smoker	289 (86.8%)	958 (88.1%)	110 (88%)	150 (89.8%)
Smoker	28 (8.4%)	68 (6.3%)	12 (9.6%)	7 (4.2%)
Missing	16 (4.8%)	62 (5.7%)	3 (2.4%)	10 (6%)
Hypertension (pre-pregnancy)				
No	299 (91.4%)	1058 (99.8%)		
Yes	28 (8.6%)	2 (0.2%)		
Diabetes (pre-pregnancy)				
No	326 (97.9%)	1085 (99.7%)	121 (96.8%)	162 (97%)
Yes	7 (2.1%)	3 (0.3%)	4 (3.2%)	5 (3%)
Other systemic inflammatory diseases				
No	325 (97.6%)	1078 (99.1%)	122 (97.6%)	159 (95.2%)
Yes	8 (2.4%)	10 (0.9%)	3 (2.4%)	8 (4.8%)
End-stage renal disease (ESRD)				
Pre-pregnancy	10 (3.2%)	0 (0.0%)		
During FU	4 (1.3%)	0 (0.0%)		

Table 7. Descriptive baseline characteristics of women with IgAN at first antenatal visit in Sweden in 1992-2015, population controls and sisters. Continuous parameters are presented as mean with SD, categorical values as numbers and percentages.

	IgAN *n* (%)	Reference *n* (%)	aOR[a] (95 % CI)	IgAN *n* (%)	Sisters *n* (%)	aOR (95 % CI)
Women	208	622		116	157	
Pregnancies	327	1060		122	160	
Births (stillbirth)	333 (2)	1088 (5)		125 (1)	167 (0)	
Pregnancies, *n*	**327**	**1060**		**120**	**162**	
Preterm birth < 37 w[e]	43 (13.1 %)	59 (5.6 %)	2.69 (1.52-4.77)	7 (5.7 %)	5 (3.1 %)	1.37 (0.24-7.73)
Medically indicated[f]	29 (8.9 %)	18 (1.7 %)	6.55 (3.02-14.2)	6 (4.9 %)	2 (1.3 %)	2.74 (0.22-34.97)
Spontaneous[g]	14 (4.3 %)	41 (3.9 %)	1.04 (0.46-2.34)	1 (0.8 %)	3 (1.9 %)	0.32 (0.01-19.47)
Very preterm < 34 w[k]	7 (2.1 %)	18 (1.7 %)	1.27 (0.52-5.34)			
Preeclampsia	45 (13.8 %)	44 (4.2 %)	4.29 (2.42-7.62)	11 (9 %)	9 (5.6 %)	2.46 (0.49-12.43)
Gestational diabetes[h]	3 (0.9 %) *n* = 320	2 (0.2 %) *n* = 1057	6.97[i] (1.21-40.21)	0 (0 %) *n* = 118	2 (1.3 %) *n* = 155	[j]
Live births, *n*	**331**	**1083**		**124**	**167**	
Neonatal death[b]	0 (0 %)	3 (0.3 %)		0 (0 %)	1 (0.6 %)	
Small for gestational age[c]	53 (16.0 %)	120 (11.1 %)	1.84 (1.17-2.88)	21 (16.9 %)	19 (11.4 %)	1.73 (0.84-3.58)
Apgar < 7 at 5 min	6 (1.8 %)	15 (1.4 %)	1.56 (0.5-4.81)	1 (0.8 %)	3 (1.8 %)	0.50 (0.03-8.92)
Cesarean section	79 (23.9 %)	175 (16.2 %)	1.74 (1.14-2.65)	24 (19.4 %)	36 (21.6 %)	0.74 (0.35-1.59)
Birth weight (g), mean (SD)	3337 (693)	3520 (596)	$p < 0.0001$			

Table 8. *Maternal and infant outcomes in pregnant women with IgAN compared to general population controls and to their sisters.*

Discussion

Main findings

IgAN, death and ESRD (study II)

We found a 53% increased mortality in a large unselected cohort of IgAN patients, compared with a matched reference population, corresponding to one extra death per 310 py and a 6-year reduction in life expectancy. The effect of IgAN on mortality was present in all age groups, in both men and women and across a vast variety of strata including in patients with the systemic IgAV form of IgAN. As expected, the increase in mortality was particularly pronounced in IgAN patients with ESRD. Importantly, our data did not indicate increased mortality in IgAN patients before progression to ESRD, and more IgAN patients reached ESRD (n = 803) than died (n = 577) during follow-up. This finding was somewhat unexpected, as cardiovascular risk factors including hypertension accumulate early in the course of IgAN,[104, 105, 130] and contrasts with previous data indicating increased mortality across all ages and in all CKD stages, and death rates vastly outnumbering ESRD incidence in unselected CKD patients.[92, 93] On the other hand, our findings are in line with the results from a register-based Norwegian study, where mortality was significantly increased only in IgAN patients with ESRD, and in IgAN individuals with a projected high risk of ESRD progression at diagnosis.[97] There is also evidence that ESRD risk exceeds death risk in non-diabetic CKD cohorts including IgAN,[95, 131] and that mortality is lower in IgAN compared with other primary glomerular diseases, despite equal or higher rate of ESRD progression, only partly explained by lower age at diagnosis.[94] The ESRD-free survival rates of 75 % at 10 years, 61 % at 20 years and 51 % at 30 years from biopsy are comparable to older studies.[9, 15]

We found an increase in death from cardiovascular disease as well as in death from 'other causes'. Cancer-related death rates were not increased compared with the matched controls or spouses. In a recent study from our study group based on the same IgAN cohort, total cancer risk was increased only after progression to ESRD, with the highest ORs for cancer types with known association to kidney transplantation.[132]

We found only a small and non-significant decline in relative mortality with calendar period. This was unexpected, as IgAN treatment has evolved during our study period, particularly with the introduction of RAASi that

have been shown to slow down eGFR decline.[62, 63] Also, according to our data mortality was not increased in IgAN patients on RAASi treatment or statins.

IgAN and IHD (study III)

Immunoglobulin A nephropathy was associated with an 86 % increased risk of (fatal or non-fatal) IHD, compared with a matched reference population. The absolute risk increase was one extra new IHD case per 338 py. An increased aHR for IHD was confirmed in men both men and women and across a wide variety of strata, as well as in secondary comparison groups (siblings and spouses). As diagnostic accuracy tend to be better for more severe diagnoses, we also studied MI separately from all IHD, finding similar increase in relative risk (83 %) with absolute risk increase of one extra incident MI in 654 py. These findings are consistent with the increased cardiovascular death rates demonstrated in study II, and with the finding of almost tripled odds for IHD in a regional Finnish study of 221 IgAN patients who had their biopsies performed between 1980-1990.[105]

IgAN and pregnancy outcomes (study IV)

In our pregnant IgAN cohort we found increase rates of preterm birth < 37 weeks' gestation (aOR 2.67). This increase was seen only for induced preterm labor; spontaneous prematurity was not increased. As there was no significant increase in very preterm birth < 34 gestational weeks. The increased rate of induced preterm labor might be related to more than fourfold odds for preeclampsia and almost doubled SGA odds, both complications than may call for intervention. However, some findings may be assuring to women with IgAN. The rates of neonatal distress (Apgar score < 7) were low and did not differ significantly between groups. The very low perinatal death rate in IgAN women (stillbirth and neonatal death < 1 %) was not different from the reference population. Except for SGA, odds ratios for all outcomes were lower when IgAN women were compared to their pregnant sisters, and did not reach statistical significance. This indicates that some of the increased risks in IgAN patients may not be due to IgAN itself, but rather be explained by genetic or environmental factors that they shared with their sisters. Interestingly, both pre-pregnancy and gestational diabetes were increased in IgAN women compared with matched controls, but not compared with their sisters.

We found very high rates of preeclampsia in women with IgAN. This must be interpreted with caution, as the definition of preeclampsia in

women with preexisting CKD is not easily defined, since its core features of hypertension and proteinuria are often already present before pregnancy. Primary preeclampsia in women without preexisting hypertension or proteinuria typically apperas early during pregnancy, and is characterized by an abnormal placentation and imbalanced levels of pro- and antiangiogenic markers, and a high risk of early fetal growth restriction and early preterm birth. On the contrary, preexisting CKD is has been linked to a "maternal" type of preeclampsia associated with a primarily normal placentation and later and milder effects on the growing fetus.[133, 134].

Study design

Study I

Study I is a validation of the IgAN diagnosis of histopathology reports by patient chart review, allowing to calculate a positive predictive value, in order to establish a nationwide cohort of IgAN patients to be used in register-based studies.

In register-based studies, patients are often identified by ICD codes in national healthcare or quality registers. However, as there is no ICD code exclusive to IgAN, such a strategy would be neither sensitive nor specific enough in this case. Since the demonstration of IgA deposits in a renal biopsy is a prerequisite for IgAN diagnosis, we instead used pathology reports to identify our patients. This was facilitated by the fact that renal biopsies are evaluated in only four pathology departments in Sweden, and that three out of four code their biopsies according to the SnoMed-CT system, where IgAN constitutes a specific entity. From the fourth lab not using SnoMed-CT codes, patients were identified by the manual screening of renal biopsy reports by an experienced renal pathologist.

Patient chart review is a standard method for diagnosis validation. An assessment of all the available data, including both patient charts with lab results and histopathology reports, were weighed and used as the gold standard for 'true' IgAN diagnosis. Hence, the factor used to define the patients (pathology reports) was not completely independent from the gold standard used. Alternative ways to validate the diagnosis could for example be by phone interviews with the patients or their physicians, or by the comparison with a quality register. However, interviews would be time consuming and bear a significant risk of recall bias. Also as we wanted to include cases from a long time period, a significant proportion of both patients and physicians could be impossible to trace or even dead. Although the Swedish

Renal Register has a high coverage for transplant recipients and patients on chronic dialysis, it is not suitable to define non-ESRD IgAN cases.

Studies II-IV

Studies II-IV were register-based, observational cohort studies. Although data were analyzed in a retrospective manner, the data were collected prospectively for the national health registers used. Through the collection of biopsy data from all the pathology labs in Sweden where renal biopsies are assessed, we could define a nation-wide IgAN cohort. As such, our cohort does not reflect the "natural history" of IgAN, but rather represents a wide range of IgAN disease severity and treatment standards, compared to if we had to collect the data ourselves, where we would have been able to include only one or maybe a few centers. Studies restricted to tertiary centers carry a higher risk of selection bias, where patients on the one hand tend to have a more severe disease, yet on the other hand might receive better treatment. The nationwide design also provided us with a very large cohort of more than 4000 IgAN patients, providing great statistical power, hence enabling us to calculate more precise risk estimates with narrower confidence intervals, and allowing for stratified analyses.

With the inclusion of individually matched reference individuals without IgAN, we were able not only to perform survival analyses with the calculation of hazard ratios, but also to estimate absolute risk differences.

Validity

The IgAN diagnosis in our studies was defined by biopsy reports. The clinical validation of a random subset of 127 patients in study I demonstrated a high internal validity, with a PPV of 95 % for a confirmed or likely 'true' IgAN. This figure could be compared to what have been found in other diagnosis validation studies based on the Swedish Inpatient Register or the CDR, showing PPVs for most somatic diagnoses of 87-99 %.[123] Generally, the more severe the disease, the more accurate the diagnosis. In one example studying MI, the diagnosis was judged to be correct in 2053 out of 2101 patients (PPV 98 %).[135] In two studies including 317 vs 17 patients with a diagnosis of heart failure, the PPV was 82-87 %, rising to 95-99 % when restricting to heart failure only as primary diagnosis,[136, 137] and rheumatoid arthritis was confirmed in 440 of 505 and 489 of 510 patients giving a PPV of 87 % and 96 %, respectively.[138, 139] As IgAN is a well-defined histopathological entity, where a renal biopsy is generally considered mandatory for diagnosis, one might have expected an even higher PPV. However, for every

diagnosis, some ambiguous cases will be misclassified at some stage, and every database will include some mechanical coding errors.

Study size and confounding

Our main cohort included 4126 patients with biopsy-verified IgAN. To our knowledge, this is the largest IgAN cohort studied to date. In study II on mortality, we included 3622 IgAN patients and 18,041 matched general population controls and in study III on IHD we included 3945 IgAN patients and 19,272 matched control subjects. We were also able to follow a large proportion of the patients for a long time, summing up total follow-up times of more than 50,000 py in IgAN patients and around 280,000 py in controls. Study IV includes more than 300 pregnancies in women with IgAN.

In every study, there is the risk of drawing wrong conclusions from the data. A type 1 error is the inference of spurious association, or more precisely an erroneous rejection of the null hypothesis, whereas a type 2 error is the opposite, i.e. to not infer an association that is actually there. Statistical significance levels are chosen to reduce the risk of random type 1 errors generally below 5 % (95 % significance level), without a too much increase in the risk of type 2 errors. Large study size and a high number of observations will increase power and hence reduce the risk of type 2 errors. This will also increase precision in the estimates with narrower confidence interval.

Type 1 and type 2 errors may also arise by confounding, i.e. non-random or systematic imbalance in the distribution of variables that affect the outcome under study and that are unevenly distributed between exposed and unexposed individuals that may lead to spurious associations (or lack of associations) between the exposure and outcome studied. As randomization is not an option in observational studies, we dealt with systematic type 1 errors through matching or statistical adjustment. On the other hand, the adjustment for a factor that is not a confounder but rather a mediator of the effect of exposure on the outcome may erroneously attenuate the risk estimates and introduce a type 2 error (over-adjustment).

In studies II and III, the risk of type 2 error is reduced by the large study size of and the abundance of the main outcomes studied (death and IHD). Our IgAN cohort was compared with a reference population matched for confounding factors that could impact the outcomes: age (both IHD and death risk increase with age), sex (IHD is more common in women than in men, who also has a lower life expectancy), calendar year (both renal biopsy practice, IgAN treatment standards, IHD incidence general population life

expectancy has changed over the years), and county of residence (to account for regional public health differences within Sweden).

As individual level income data are not available in the TPR, we used educational level as a proxy for socioeconomic standard. There is massive evidence that low income and low educational level are both independently associated with IHD and death, in part due to differences in health behavior. Social deprivation has also been associated with higher IgAN incidence and renal biopsy rates.[27] We chose to adjust also for the presence at baseline (i.e. *before* renal biopsy) of diabetes and systemic inflammatory diseases that might influence outcome without being directly caused by IgAN. We found about doubled and tripled rates of inflammatory diseases in IgAN patients compared with in controls. It could be disputed whether this is in part to be considered an over-adjustment, since these comorbidities might be causally associated with IgAN in ways that are not fully understood. For example, an increased incidence of IgAN has been demonstrated in patients with inflammatory bowel disease,[140] and genome-wide association studies suggest that some genetic risk are shared between IgAN and auto-immune diseases including inflammatory bowel disease, SLE and hypothyreoidism.[141]

In study II, we adjusted also for CVD in broad sense. This included also hypertension. As IgAN may be symptomatically for years and as such contribute to hypertension long before renal biopsy is performed, hypertension and maybe also CVD might rather be considered as mediators between IgAN and death rather than confounders. When adjusting for all covariates except cardiovascular disease, death aHR increased from 1.54 to 1.74, which might be closer to the true HR. Omitting also diabetes from the model changed the aHR only marginally to 1.79, and unadjusted HR was 1.83. Since the NPR includes only hospital-based diagnoses, and hypertension is mainly treated in primary health care, rates may be largely underestimated in the control-group compared with in IgAN patients, who generally are cared for in hospitals. In study III, we revised the Cox model so that HRs were adjusted for CVD other than IHD and hypertension.

The statistical models were adjusted for smoking habits and BMI in study IV, but not in study II and III, as these data are available in the MBR, but not in the other registers used for our studies. As smoking is a strong predictor of IHD and death, this might lead to either over- (type 1) or underestimation (type 2), if smoking habits differ between IgAN patients and matched controls. In our pregnancy cohort, the proportion of smokers did not differ significantly between women with IgAN (8.4 %) and their controls (6.3 %; $p = 0.18$) and an earlier Swedish study found equal rates of

smokers (14.3 %) among 70 IgAN patients and 70 age- and sex-matched controls. This indicates that any difference in smoking habits is unlikely to have significantly affected our results.[142]

As IgAN patients might differ from the control group in aspects that are nor matched on nor adjusted for, we made secondary comparisons with siblings and spouses who are likely to share environmental (and genetic in siblings) risk factors with their IgAN patient counterpart. These analyses gave very similar risk estimates for both death and IHD as in the main analyses, reducing the possibility that the observed risk increase be due to residual intra-familial confounding.

Since our cohort was large, there was room for stratified analyses. For death, ESRD, IHD and MI, the aHRs were higher during the first year of follow-up. One explanation might be that a renal biopsy might have been performed as part of the investigation of patients with severe illness and a high probability of adverse outcomes within a year. This finding might also reflect a subpopulation with a particularly aggressive IgAN phenotype. Even though not statistically significant, there was a trend towards higher aHRs risks for death, IHD and MI with lower educational level and for death, ESRD and IHD (but not for MI) in non-Nordic immigrants, possibly reflecting differences in health-related behavior and healthcare accessibility.

Study III on pregnancy outcomes is substantially smaller, with an 80 % power to detect a 44 % increase in the rate of preterm birth at the 95 % significance level, and a lower power to detect more rare outcomes. Still, this is the largest pregnant IgAN cohort that we are aware of. We included both singleton and multiple pregnancies. Since the MBR contains information on both smoking habits and BMI, these were statistically adjusted for in the logistic regression model.

Bias and misclassification

Main exposure: IgAN

In our studies, IgAN was defined through renal biopsy findings. The validation of IgAN in study I showed a low probability of false positive IgAN. All patient charts were reviewed by the same researcher (myself). As this was made without blinding for pathology reports, some bias could not be ruled out. To reduce this risk, all ambiguous cases were discussed with an experienced nephrologist (Sigrid Lundberg), and final classification decided by consensus. Validation was based on patient chart recorded in "real time", and recall bias should not be an issue. The national and population-

based design also should decrease the risk of bias towards more severe IgAN cases, compared with single center studies, that might over-sample cases referred for tertiary care. Still, as IgAN might be completely asymptomatic, there is a risk that patients with mild disease might not undergo biopsy. This is even especially the case in patients with IgA vasculitis (IgAV//HSP), where the combination of glomerulonephritis and extra-renal manifestations may point to IgAN also without a renal biopsy. In fact, current Swedish and international IgA vasculitis guidelines recommend renal biopsy only in ambiguous cases or if there is high risk of progressive or permanent kidney damage.[143, 144] However, our sub-group analyses of patients with IgA vasculitis indicate similar HR:s for both death and IHD as in all IgAN patients.

Outcome variables

A proportion of IgAN patients (2.7-2.8 %) and control subjects (3.7-3.8 %) emigrated from Sweden before end of follow-up (May 31, 2017). The difference between the groups is small, and most likely mainly reflects the higher death rates in IgAN patients, though a lower inclination among people with chronic illness to move abroad could also be hypothesized. We could not exclude that rates of death, ESRD or IHD differed has a different distribution in emigrants, though the small difference in emigration rates makes this unlikely to have significantly biased our results.

The very high data quality in the TPR, with virtually complete all death reported within 30 days, ensures extremely low misclassification of this outcome.[125] For cause-specific death based on the CDR, classification is mainly based on the judgment of the physician confirming the death or responsible for the care of the patient and only to a small extent by autopsies which gives room for some misclassification.[126] However, a register validation has demonstrated high accordance with death cause based on patient records for cardiovascular (87 %) and cancer-related (90 %) deaths.[145]

Our definition of ESRD was based on the occurrence the ICD diagnosis codes for CKD stage 5 in either the NPR or the CDR, and diagnosis or procedure codes in the NPR for kidney transplantation and chronic dialysis. For dialysis, ESRD was defined as the occurrence of any of the corresponding codes at least three times over at least four months. This conservative approach was used to minimize the inclusion of patients requiring short-time dialysis due to acute kidney damage. As a consequence, patients who died within four months of onset of chronic dialysis might be misclassified as not reaching ESRD. However, these patients will still contribute to the composite outcome of death or ESRD in the study II. The incidence of ESRD

was 260 per million py in our reference population, with a median age of 38.7 years at inclusion. This can be compared to a Swedish national yearly incidence of RRT at 111 per million py in 2019; 61 per million py in persons < 65 years and 314 in persons ≥ 65 years, with median age at RRT start of 63 years, according to the Swedish Renal Registry annual report.

Ischemic heart disease was defined by relevant ICD codes in the PDR. Validation studies have confirmed very high specificity of a MI diagnosis in the NPR (PPV = 98 %)[135] and in a smaller study angina pectoris (PPI = 95 %).[123] Diagnostic sensitivity is more difficult to determine, as a true gold standard is hard to establish. However, studies suggest sensitivities of 77-91 % for MI. The inclusion also of the corresponding diagnoses from the CDR should increase sensitivity. An awareness among IgAN patients and their care providers of an increased risk of IHD associated with CKD could possibly introduce surveillance bias, more so for angina pectoris than for MI, where symptoms tend to be more severe and diagnostic accuracy higher. Our finding of almost identical aHRs for MI (1.83) and unselected IHD (1.86) suggests such bias is not a substantial feature.

For hypertension, a high degree of both surveillance bias and detection bias could be expected, as IgAN patients are much more prone to have their blood pressure measured than the general population and also are generally cared for in hospitals, while controls with hypertension may be followed in primary health care that do not report to the NPR. Our inclusion of data from the PDR on antihypertensive medications will only partly compensate for this, as hypertension is treated more aggressively with generally stricter blood pressure goals in patients with CKD including IgAN.

For pregnancy outcomes, preterm birth and SGA are identified by well-defined criteria based on birth weight and dates of birth and conception, with very low risk of misclassification. For preeclampsia, we relied on the corresponding ICD code in the MBR or NPR as registered by the obstetrician. The definition of preeclampsia in patients with CKD including IgAN is challenging, as the diagnosis was based on the occurrence during pregnancy of hypertension and proteinuria, which are also common features of IgAN.

Generalizability

Our studies are based on a clinically validated, nationwide renal biopsy cohort, and takes advantage of population-based population and healthcare registers. The IgAN cohort had very similar background characteristics compared with the Norwegian cohort studied by Knoop et al[97] (mean age

40 vs 39 y, 30 % vs 26 % women, 32-62 % vs 45 % with hypertension at inclusion). The lower age (mean 33 y) and more equal sex distribution (50 % women) in the Korean study by Lee et al might explain the somewhat lower mortality rates. Diabetes was also about twice as common in our cohort, compared with the Korean and Norwegian studies. We have data on eGFR only for a limited subset of patients selected for diagnosis validation, with a mean eGFR of 75 mL/min/1.73m^2 and 60 % and 59 % with CKD stage 1-2, compared to a mean eGFR of 68 mL/min/1.73m^2 in Knoop and Lee.

There are some limitations concerning to what extent our results can be generalized to other health care systems. Firstly, for the main part of the study period, Sweden had an ethnically rather homogenous population of mainly Caucasian origin, and our results may not be fully relevant to Asia or the Americas. Studies from Japan, China and South Korea higher rates of disease progression than European studies, hence our data might underestimate the risk of progression to ESRD in an East-Asian population. Secondly, Sweden is a high-income country with a mainly publicly funded health-care highly accessible also to less wealthy citizens and prescribed drugs are subsidized. IgAN prognosis might differ in a low-income setting or where healthcare is less equally accessible.[146] Sweden has also a good general health status, low tobacco use and a very good reproductive health, with among the lowest perinatal mortality rates in the world.[147] Thirdly, even though a fairly large share of the IgAN in our validation study were identified through screening, we did probably under sample mild or early cases compared to for example Japan, where urine dipstick screening is regularly performed in school and occupational healthcare.[90] Fourthly, our data are do not reflect the natural course of IgAN but rather patients treated according to the current praxis of the time, and may not be valid in different treatment traditions.

Clinical implications and future perspectives

This thesis demonstrates substantial evidence of the associations with IgAN and increased risks of death, ESRD and IHD including MI. The nation-wide population based approach provided us with an unusually large IgAN cohort, and combined with the inclusion of individually matched reference populations we were able to determine both relative and absolute risk estimates with high precision. In that way, these studies contribute to the estimation of the impact of IgAN on morbidity and mortality at a population level.

As we lack data on important risk markers of IgAN such as blood pressure, proteinuria, eGFR and histopathologic picture, we were not able to make precise predictions of IgAN prognosis on an individual level. In the last decades, much IgAN research has sought to identify risk markers for IgAN disease progression in order to develop prediction tools to promote individual risk assessment in relation to ESRD.[18, 22, 23, 148] Our finding that ESRD is a strong predictor of mortality in IgAN, and that mortality might not be increased before reaching ERSD, makes such predictions even more relevant, and may be assuring to IgAN patients with projected low risk of progression. The increased death and IHD risks in IgAN patients suggest that theses outcomes be included studied in relation to known IgAN progression markers, in order to ideally include both death and IHD risks in future developments of the IgAN prediction tool.

Our data on medication is prone to indication bias, in that guidelines promote RAASi mainly in patients with risk factors (hypertension end significant proteinuria) and immunosuppressive agents preferentially in patients with more severe disease.[61] This bias may to some extent be balanced by a counter-effect of drug withdrawal in very sick patients unable to tolerate such medications. Still, our finding that IgAN mortality was not increased in patients on RAASi (aHR 0.80, n.s.) or statins (aHR 0.83, n.s.) compared to matched controls is interesting, especially as mortality in fact was increased in patients on other medications, including non-RAASi antihypertensive drugs. While there is robust evidence for a beneficial effect of RAASi on IgAN progression,[62, 63] the same is not true for statins.[61, 72, 142] Our data suggest a possible beneficial effect of statins should be addressed in future research.

Our data support the current practice that women with IgAN should receive close follow-up during pregnancy,[112, 117, 149] as we found increased risks of preterm birth, gestational diabetes, low birth weight and a very high risk of preeclampsia. Even so, most women experienced a favorable pregnancy outcome. The low rates of very preterm birth, low Apgar score and progression to ESRD during pregnancy, and the very low rates of stillbirth and neonatal death that were not increased compared with women without IgAN are very assuring, at least for women living in a high-income context.

Conclusions

Based on the studies included in this thesis, the following main conclusions may be suggested:

In Sweden, renal biopsies consistent with IgAN have a high predictive value for the diagnosis of IgAN. Patient characteristics of individuals with biopsy-verified IgAN are similar to that reported from international literature.

A biopsy diagnosis of IgAN in Sweden is associated with a 53% increased mortality. The absolute excess risk corresponds to one extra death in 310 person-years, with a 6-year reduction in life expectancy.

Excess mortality in IgAN appears to be mainly associated with end-stage renal disease and renal replacement therapy.

IgAN is associated with an 80 % increased risk of ischemic heart disease compared with an absolute excess risk corresponding to one new ischemic heart disease event in 344 person-years.

Most women with IgAN in Sweden experience a favorable pregnancy outcome, but these women are nevertheless at a moderately increased risk of late preterm birth and intrauterine growth restriction and a high risk of preeclampsia.

Sammanfattning

Den här avhandlingen syftar till att utifrån nationella register belysa i vilken grad den kroniska njursjukdomen IgA-nefrit (IgAN) leder till förtidig död, terminal njurskada hjärt-kärlsjukdom och graviditets- och förlossningskomplikationer i jämförelse med personer utan IgAN.

Kronisk glomerulonefrit är långvarig inflammation i njurens inre där blodet filtreras. IgA-nefrit (IgAN) är den vanligaste formen av kronisk glomerulonefrit världen över och drabbar årligen omkring 2-10 personer per 100000. Symtombilden varierar stort. De flesta har mikroskopiskt läckage av blod och protein till urinen, i många fall med episoder av synligt blod i urinen vid infektioner. Högt blodtryck är vanligt. Förloppet varierar från asymtomatiskt med stabil njurfunktion till progressivt med tilltagande njurskada och i enstaka fall stormande med akut njurskada. Omkring 35 % når terminal njurskada med behov av dialys eller transplantation inom 20 år från upptäckt. För diagnos krävs att immunglobulin A (IgA) påvisas i vävnadsprov från njuren (njurbiopsi). IgA-vaskulit (IgAV) eller Henoch-Schönleins purpura (HSP) är en särskild form av IgAN som också drabbar huden, ofta även leder och tarm. Hos barn är IgAV den vanligaste formen av IgAN.

Det är tidigare känt att kronisk njurskada ökar risken för högt blodtryck, hjärt-kärlsjukdom och död, med högre risk ju lägre filtreringsförmåga (GFR) som njuren bevarat. Nedsatt njurfunktion medför även ökade graviditetsrisker. Kunskap specifikt kopplad till IgAN är begränsad.

Alla fyra studier i den här avhandlingen utgår från samma grupp patienter med IgAN, sammanställd för ett tidigare arbete. Genom datoriserad sökning i samtliga njurbiopsisvar från de fyra patologavdelningar i Sverige som bedömer alla njurbiopsier sammanställdes en kohort med 4126 individer som fått biopsidiagnosen IgAN mellan 1974 och 2011.

Tack vare nationella register av god kvalitet med hög täckningsgrad kopplade till personnummer lämpar sig Sverige väl för epidemiologisk forskning. För avhandlingens arbeten har vi länkat data från IgAN-kohorten till Registret över totalbefolkningen (I-IV), Patientregistret (tidigare Slutenvårdsregistret) (II-IV), Dödsorsaksregistret (II-IV), Läkemedelsregistret (II-III) och Medicinska Födelseregistret (IV).

Studie I syftar till att validera biopsidiagnosen IgAN genom jämförelse med uppgifter i patientjournalen. Från IgAN-kohorten valdes slumpvis 127 patienter ut för journalgranskning enligt ett standardiserat protokoll. Av dessa

bedömdes IgAN säkert bekräftad i 116 fall (91 %) och mest sannolik diagnos i ytterligare fem fall (4 %). Sammantaget bedömdes biopsidianosen IgAN korrekt i 95 % (91-99 %) av fallen. I tre fall bedömdes diagnosen inkorrekt och i ytterligare tre fall bedömdes en annan diagnos mer sannolik än IgAN. 74 % var män, medelåldern vid diagnos 39,6 år. Den vanligaste sökorsaken var synligt blod i urinen, därefter utredning av högt blodtryck eller avvikelser vid rutinmässig urinprovtagning.

I studie II studerade vi dödlighet och utveckling av terminal njurskada hos individer med 3622 individer med IgAN jämfört med 18.041 köns- och åldersmatchade individer utan IgAN genom överlevnadsanalys. Patienter och kontroller med terminal njurskada före biopsidatum uteslöts ur analysen. I gruppen med IgAN inträffade ett extra dödsfall per 310 personår, vilket motsvarade en genomsnittlig livsförkortning på sex år och en relativ ökning av dödligheten med 53 %. Dödligheten var signifikant ökad endast hos patienter som fortskred till terminal njurskada. Patientöverlevnad utan terminal njurskada var 75 % efter 10 år, 61 % efter 20 år och 51 % efter 30 år.

Studie III undersökte ischemisk hjärtsjukdom (kärlkramp och hjärtinfarkt) hos 3945 individer med IgAN i jämförelse med 19.272 ålders- och könsmatchade referensindivider genom samma typ av överlevnadsanalys som i studie II. Patienter och kontroller med ischemisk hjärtsjukdom före biopsidatum utesluts ur analysen. En riskökning för nydiagnostiserad kärlkramp eller hjärtinfarkt på 1 per 337 personår sågs i kohorten med IgAN, med en relativ riskökning på 86 %. Motsvarande värden för enbart hjärtinfarkt var 1 per 655 personår och en relativ riskökning på 83 %.

I studie IV jämfördes graviditets- och förlossningsutfall för 327 graviditeter hos 208 kvinnor med IgAN med 1060 graviditeter hos 622 kvinnor utan IgAN genom logistisk regression. 13.1 % av graviditeterna vid IgAN avslutades före fullgången tid (37 veckor), jämfört med 5.6 % i referensgruppen. En riskökning såg endast för förtidig förlossning genom igångsättning eller kejsarsnitt; risken för spontant tidig värkstart eller mycket tidig förlossning före 34 fulla graviditetsveckor var inte ökad. Kvinnor med IgAN fick mycket oftare havandeskapsförgiftning och födde oftare barn med låg födelsevikt. Dödfödda barn och dödsfall hos nyfödda var mycket få, och inte vanligare hos kvinnor med IgAN än kvinnor utan IgAN.

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