Risk factors of chronic kidney disease progression: Dutch cohort studies

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Chapter 1

– Introduction

THE KIDNEY AND KIDNEY DISEASE

Kidneys filter waste products and toxins from the circulation, maintain fluid balance, regulate blood pressure, and are involved in bone mineralisation and erythropoiesis, amongst other things. Disturbances in kidney function may lead to a variety of problems. Healthy kidneys are of vital importance for both our physical and mental wellbeing.

Kidney function is determined by the rate at which the functional units of the kidney, the glomeruli, filter the blood. This glomerular filtration rate (GFR) is measured in mL per minute, usually adjusted for body surface area. Measuring GFR is relatively expensive and time-consuming. Therefore, both in clinical and research setting, GFR is usually estimated (eGFR) by formulae, rather than measured.

Naturally, kidney function deteriorates with age, with about 1 mL/min/1.73m^2 per year after age 40.[1, 2] On average, healthy individuals have a GFR of 100 to 120 mL/min/1.73m^2. Due to the slow rate of kidney function decline, the majority of people will not experience any clinically relevant kidney disease. Kidney function is classified according to chronic kidney disease (CKD) stage 1 to 5 (Table 1). Progression to worse CKD stages is associated with higher risk of end-stage renal disease (ESRD), cardiovascular morbidity, and all-cause and cardiovascular mortality.[3, 4] Clinically relevant CKD is often defined as CKD stage 3 (eGFR <60 mL/min/1.73m^2) or higher. The consequences of CKD stage 3 depend on an individuals' age. For an 80-year old individual CKD stage 3 may be simply the consequence of ageing. In contrast, for a 40-year old individual, further deterioration of kidney function in following decades may eventually lead to ESRD, substantially increasing the risk do die prematurely. Nonetheless, on average a lower kidney function increases cardiovascular and mortality risk also in older populations.[4]

Table 1: Chronic kidney disease (CKD) classification, based on estimated glomerular filtration rate (eGFR).

CKD stage	eGFR (mL/min/1.73m^2)	Terms
1	≥ 90*	Normal or high
2	60 to 89*	Mildly decreased
3a	45 to 59	Mildly to moderately decreased
3b	30 to 44	Moderately to severely decreased
4	15 to 29	Severely decreased
5	< 15	Kidney failure

* CKD stage 1 and 2 are also characterized by albuminuria.

Globally, the prevalence CKD has reached epidemic proportions, and kidney disease is responsible for considerable health care costs and loss of disability adjusted life years. In Europe 11% of the population aged 45 years or older meets the criteria for CKD stage 3.[5] In the United States this is about 44% of the population aged at least 65 years.[6] In 2016, chronic kidney disease caused 1.2 million deaths worldwide, being the 12th cause of death. In contrast, in 1990 chronic kidney disease was the 27th cause of death.[7] The increasing prevalence of CKD can be explained by population ageing, higher prevalence of cardiovascular risk factors, and unhealthier lifestyle the past decades. Given the still continuing trends of ageing, and the difficulty reversing unhealthy lifestyle patterns, the burden of CKD is expected to rise further.

RATIONALE FOR THIS THESIS

Several factors increase the risk of CKD and often risk factors operate complementary. A multitude of risk factors have been investigated in healthy individuals or in relation to cardiovascular disease. But their role in the progression of CKD in patients at high cardiovascular risk is less well documented. The fact that the number of cardiovascular high risk patients will only keep growing, stresses the necessity to explore the role of risk factors in this specific group. An additional challenge in cardiovascular high risk patients is that they often use a variety of cardiovascular drugs. Especially in these medicalized patients, often using multiple cardiovascular medications, it remains unclear whether cardiovascular risk factors still play a significant role in the progression of CKD. This thesis evaluates multiple risk factors for CKD, and focusses mainly, but not solely, on high risk cardiovascular patients on extensive cardiovascular treatment. Ultimately, expanding our knowledge in this field, may facilitate development of treatments specifically tailored to patients at high cardiovascular risk and aid in the development of future guidelines.

OUTLINE OF THIS THESIS

Traditional risk factors

Traditional risk factors for cardiovascular disease, such as diabetes mellitus, hypertension, and cigarette smoking, are important drivers of CKD. Hypertension and diabetes account for about 36% of the age-standardized mortality rate due to CKD. The contribution of diabetes to CKD-related mortality

doubled the past 30 years.[8] Chronic hypertension may lead to progressive glomerular and interstitial fibrosis by increasing glomerular pressure, which results in endothelial dysfunction and loss of adequate auto-regulation.[9] Renal effects of diabetes may present as diabetic nephropathy, a complex and progressive disease characterized by both structural and functional changes of the kidney. These changes encompass basement membrane thickening, glomerulosclerosis, interstitial fibrosis and tubular atrophy.[10] In the early course of diabetic nephropathy, glomerular hyperfiltration is present, which in later stages evolves into a rapid decline of kidney function and progressive proteinuria. Diabetes can be divided into type 1 and type 2 diabetes. Type 2 diabetes, the most prevalent type (about 90% of diabetes cases), usually develops after age 45 as a result of unhealthy lifestyle.[11] In contrast, type 1 diabetes is caused by an auto-immune response against the pancreatic β-cells. Type 1 diabetes generally develops in childhood or adolescence and is much rarer, comprising 5-10% of all diabetes cases worldwide.[11] Though hypertension and diabetes are strong risk factors of CKD, they only explain part of all CKD cases.

Lifestyle

Lifestyle represents another important contributor of CKD progression. Given the increasing burden of cardiovascular morbidity, population ageing, polypharmacy, and rising healthcare costs, non-pharmacological interventions form an appealing opportunity for both prevention and attenuation of chronic diseases such as CKD.

Various components of lifestyle have been gaining increasing interest the past decades, such as obesity, lack of physical activity, smoking, alcohol consumption, and dietary pattern. Obesity is ranked in the top 5 risk factors for death worldwide, and the prevalence of overweight and obesity has been rising steadily.[12] Obesity promotes kidney disease via different mechanisms. It may cause CKD directly by creating an inflammatory environment resulting from accumulation of visceral fat and by inducing chronic hyperfiltration.[13] Obesity also promotes cardiovascular disease, hypertension, and diabetes, thereby indirectly increasing CKD risk.[12] In **Chapter 2** the role of several cardiovascular and lifestyle factors in post-myocardial infarction patients is discussed. We investigated whether type 2 diabetes, hypertension, obesity, and smoking were associated with CKD progression, and whether having more risk factors led to a faster loss of kidney function. In addition, because of the complexity of obesity as a risk factor, it's role in kidney disease progression is investigated in more detail in a separate chapter, **Chapter 3**.

Dietary pattern

As an underrecognized part of lifestyle, dietary pattern is increasingly regarded a potential modifiable risk factor influencing CKD progression. Protein restriction as a reno-protective measure is adapted in nephrology guidelines, mostly for patients with advanced CKD or at high risk for CKD.[14] Dietary protein may damage the kidney by mechanical stress, and by promoting glomerular hyperfiltration through dilation of the afferent glomerular arteriole, thus increasing glomerular pressure.[15] Protein can be of animal or plant sources, and some studies suggested that protein from animal sources is more detrimental than protein from plant sources.[16] However, firm evidence regarding differential effects of animal and plant protein is lacking. Moreover, no nephrological recommendations exist regarding protein intake in individuals with a normal or slightly lower kidney function. In **Chapter 4** the potential role of high protein intake on the rate of kidney function decline is investigated in post-myocardial infarction patients.

Type 1 diabetes

Type 1 diabetes, starting at young age, comes with a 7% cumulative risk of developing ESRD within 30 years. Though dialysis postpones death from ESRD, kidney transplantation substantially improves life expectancy and quality of life.[17, 18] Additionally, simultaneously transplanting a pancreas and a kidney would not only partially restore kidney function, but also restores endogenous insulin production. The latter abolishes the need for insulin medication and prevents further progression of diabetic complications. However, transplanting a pancreas in addition to a kidney also increases risk of complications and peri-operative mortality.[19] To date, it remains controversial whether a simultaneous pancreas kidney transplantation should be preferred over transplanting a kidney alone. In **Chapter 5**, we used nationwide registry data of all type 1 diabetes patients from The Netherlands requiring renal replacement therapy, to compare survival after simultaneous pancreas kidney transplantation, kidney transplantation from a living donor, and kidney transplantation from a deceased donor.

Dyslipidemia

Hypercholesterolemia is also regarded a traditional cardiovascular risk factor, but in contrast to diabetes and hypertension, seems to be of minor importance for CKD progression.[20] Interestingly, cholesterol-lowering drugs (statins) have been shown to beneficially affect kidney function, independent of cholesterol levels. Owing to these pleiotropic effects, statins are nowadays routinely prescribed to CKD patients, and these drugs are in the top 5 of most prescribed

medications worldwide.[21, 22] Till date it remains unknown which statin and dosage, if any, has superior reno-protective properties. **Chapter 6** provides a network meta-analysis specifically addressing this question.

Acute kidney injury

CKD may also be preceded by acute kidney injury (AKI). AKI is a sudden episode of kidney failure, accompanied by rising serum creatinine levels and oliguria, and increases risk of ESRD and mortality. AKI often results from medical care, such as nephrotoxic medication or peri-operative hypoperfusion. The latter is especially relevant for cardiovascular patients. Cardiovascular disease may lead to coronary artery stenosis and myocardial infarction. Post-myocardial infarction patients have a two-fold faster annual kidney function decline, compared to the general population.[23] More importantly, cardiac surgery poses an additional risk. During cardiac bypass surgery a patient's circulation is maintained by a heart-lung machine (cardiopulmonary bypass), increasing AKI risk due to renal hypoperfusion. Depending on the cause, AKI may be difficult to treat, especially when it is not diagnosed at an early stage. At this time, there are no routinely used biomarkers available for the early identification of AKI, but recently several potentially useful markers have been described. **Chapter 7** focusses on these new biomarkers, IGFBP7 and TIMP-2, and considers their potential for predicting AKI after cardiac surgery. Early identification of AKI facilitates more effective treatment and reduces the risk of progression to CKD.

Birth weight

Finally, chronic diseases such as CKD may originate from early fetal life. The Barker hypothesis states that fetal undernutrition during gestation impacts a multitude of developmental processes, leading to higher susceptibility to both physical and mental health problems in later life.[24] For instance, individuals with low compared to normal birth weight have been shown to be more susceptible to develop diabetes, hypertension, and obesity. In relation to CKD, Brenner hypothesized that individuals with a low compared to normal weight at birth, have relatively less nephrons, which over time leads to chronic hyperfiltration.[25] Additionally, relatively smaller kidneys have less overcapacity to compensate in case of kidney damage. However, evidence of a causal association between birth weight and CKD is lacking, since current observational studies on this subject are limited by confounding. In **Chapter 8** we discuss the influence of low birth weight on kidney function at middle-age in a cohort of healthy individuals. To better estimate a causal relation between birth weight and kidney function, we performed two-sample Mendelian randomization analyses using 59 genetic variants associated with birth weight as instrument. Mendelian randomization

exploits the fact that an individuals' genetics are randomly distributed during conception, thus mimicking the randomization procedure of a randomized trial.

SUMMARY OF AIMS PER CHAPTER

Chapter 2 To investigate the association of classic cardiovascular risk factors, and the number of risk factors, with annual kidney function decline, in post-myocardial infarction patients.

Chapter 3 To investigate the association of obesity with annual kidney function decline, in post-myocardial infarction patients.

Chapter 4 To investigate the role of dietary intake of total protein, and protein from animal or plant sources, regarding annual kidney function decline, in post-myocardial infarction patients.

Chapter 5 To investigate in type 1 diabetes patients whether simultaneous pancreas kidney transplantation leads to better survival compared to a kidney transplantation alone, either from a deceased or living donor.

Chapter 6 To investigate the effect of statin use on the rate of kidney function decline and progression of proteinuria, and to gain insight into which statin would be a superior choice, from a kidney perspective.

Chapter 7 To investigate the potential added value of two novel urinary biomarkers, IGFBP7 and TIMP-2, in predicting acute kidney injury, in post-cardiac surgery patients.

Chapter 8 To investigate the association of low birth weight with kidney function at middle-age, using three different methodological approaches. In the Netherlands Epidemiology of Obesity study we performed regression analyses, and two-sample Mendelian randomization analyses using a genetic risk score for birth weight as instrument. In publicly available data we performed a two-sample Mendelian randomization study using summary level data.

Chapter 9 A general discussion about the main conclusions of the various chapters in this thesis, and the implications for clinical practice and future directions.

OVERVIEW OF USED DATA SOURCES

Alpha Omega Cohort (AOC)
The AOC is a prospective cohort of 4837 Dutch patients, aged 60-80 years, with a clinically diagnosed myocardial infarction up to 10 years before study entry. Patients were on standard cardiovascular drug treatment, in accordance with the latest international guidelines. During the first 41 months of follow-up, patients took part in an experimental study of low-dose omega-3 fatty acids (Alpha Omega Trial).[26] The trial started in 2002 and ended in 2009. Major exclusion criteria were severe heart failure, unintended weight loss of at least 5 kg the previous year, and diagnosis of cancer with a life expectancy less than 1 year. For the analyses in **Chapters 2, 3, and 4**, we included all patients with available serum samples at baseline and after 41 months of follow up, about half of the cohort. Since this selection was a random sample of the total study cohort, no bias was introduced.

Netherlands Organ Transplantation Registry (NOTR) and Renal Replacement Registry in The Netherlands (RENINE)
The NOTR is a registry of kidney transplant patients from all eight Dutch kidney transplant centers. The NOTR is a mandatory registry, coordinated by the Dutch Transplant Foundation. The registry contains information on various donor and recipient characteristics, and is updated annually. The RENINE database contains data of all patients with renal failure who need renal replacement therapy. Registration of patients is mandatory for dialysis centers, in order to receive funding. Data quality of the NOTR and RENINE is checked periodically by on-site polls, application rules, and cross checks between both registries. In **Chapter 5**, both registries were linked, resulting in a combined dataset including all Dutch type 1 diabetes patients who commenced renal replacement therapy (dialysis or transplantation) between January 1986 and January 2016 (n=2833).

Cohort of elective cardiac surgery patients at the Intensive Care Unit
This single-center cohort included 812 consecutive patients aged 18 years or older, undergoing elective cardiac surgery at the Leiden University Medical Center, The Netherlands, between December 2006 and August 2010. Exclusion

criteria were pregnancy, active infection, and emergency surgery. According to usual clinical practice, after cardiac surgery patients stayed in the intensive care unit (ICU) for post-operative care. When hemodynamic and respiratory stable, patients were transferred to the thoracic surgery ward. In **Chapter 7**, we analyzed all patients with a complicated ICU stay, defined as staying at the ICU at least 48 hours, and chronologically matched an equal number of patients with an uncomplicated ICU stay.

Netherlands Epidemiology of Obesity study (NEO)
Data of the NEO study, conducted between 2008 and 2012, was used in **Chapter 8**. It is a population-based, prospective cohort study designed to investigate pathways that lead to common disorders.[27] The NEO study included 6671 individuals aged 45–65 years, with an oversampling of overweight or obese individuals. Men and women aged 45-65 years with a self-reported body mass index (BMI) ≥27 kg/m^2 living in the greater area of Leiden were eligible to participate. In addition, all inhabitants aged 45-65 years from one municipality (Leiderdorp) were invited to participate irrespective of their BMI, allowing a reference distribution of BMI. To maintain generalizability towards the general population, analyses in the NEO study were weighted towards the BMI distribution of the general Dutch population.

Summary statistics data: GWAS on birth weight, CKDgen consortium
The instrument for birth weight that we used for Mendelian randomization analyses in **Chapter 8** was based on 59 genetic variants reaching genome wide significance in a Genome-Wide Association Study (GWAS) on birth weight published by Horikoshi *et al.* in 2016.[28] The GWAS included birth weight data from 37 studies comprising 153,781 individuals of multiple ancestries.

In the two-sample Mendelian randomization analyses using summary level data in **Chapter 8**, we used publicly available data from the CKDgen consortium on the associations of each genetic variant with eGFR.[29] The CKDgen consortium includes 133,814 participants of European ancestry from 70 population-based studies, with mean age between 50-60 years and a 5-20% CKD prevalence, defined as an eGFR <60 mL/min/1.73m^2.

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