Chronic kidney disease

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General introduction and thesis outline

CHAPTER 1

Introduction

For centuries, it has been known that health disparities exist across socioeconomic groups[1]. Higher rates of disease and shorter lifespans are observed among those with lower socioeconomic status. Despite attempts to systematically reduce these disparities, they persist to this day[2,3]. These disparities are also observed for kidney disease. Those with lower education, lower income, lower occupational level, and from deprived communities, are observed to be at higher risk of chronic kidney disease (CKD)[4-6]. The mechanisms that link low socioeconomic status to CKD are not fully understood. This thesis is an effort to increase our understanding of socioeconomic disparities in kidney disease. In particular, I seek to apply modern concepts from genetic epidemiology to answer social epidemiological questions in the context of CKD. In this first chapter, I discuss background and core concepts, identify knowledge gaps, and describe aims and hypotheses. Finally, I provide an outline of this thesis.

Epidemiology of chronic kidney disease

CKD is a heterogeneous group of disorders marked by progressive loss of kidney function and/or signs of kidney damage. Currently, the international guideline group *Kidney Disease: Improving Global Outcomes* defines CKD as the presence of abnormalities of kidney structure or kidney function of any cause, that exist for at least 3 months[7,8]. It is associated with cardiovascular and all-cause mortality[9,10], and it may eventually progress to end-stage renal disease which requires renal replacement therapy (i.e. dialysis and kidney transplantation). CKD staging is based on risk classification of cardiovascular events and end-stage renal disease, and is currently determined by a combination of level of kidney function (assessed by estimated glomerular filtration rate, eGFR) and kidney damage (assessed by albuminuria) (**Table 1**). It is estimated that CKD affects 11-13% of the global population[11]. The incidence of CKD is increasing. Extrapolating from current trends, it has been projected that 50% of the US population will eventually develop some stage of CKD during their lifetime[12]. As such, CKD poses a major burden on patients and global health resources.

Traditional cardiovascular risk factors such as older age, overweight, and smoking predispose to CKD[13,14] but only explain a relatively small percentage of CKD cases. The most important risk factors for CKD are diabetes and hypertension, which together explain 50-70% of cases. However, it has been observed that CKD can

also occur in the absence of diabetes and hypertension[15]. Thus, a large proportion of CKD cases remains unexplained, warranting the identification of additional, non-traditional risk factors.

Table 1. Prognosis of CKD by categories of GFR and albuminuria. CKD is defined as abnormalities of kidney structure or function present >3 months, decreased GFR <60mL/min/1.73m² (G3) and/or at least moderately increased albuminuria (A2). Darker coloring indicates higher risk of cardiovascular events and end-stage renal disease. Adapted from KDIGO 2012.

					Persistent Albuminuria Categories		
					Description and range		
					A1	A2	A3
					Normal to mildy increased	Moderately increased	Severely increased
					<30 mg/g	30-300 mg/g	>300 mg/g
					≤3 mg/mmol	3-30 mg/mmol	>30 mg/mmol
GFR Categories (mL/min/1.73m²)	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			

Socioeconomic disparities in risk of CKD

Socioeconomic status, also referred to as socioeconomic position or social class, represents one's access to social and economic assets and resources[16].

CKD is unequally distributed across socioeconomic groups. Higher prevalence and incidence rates of CKD and end-stage renal disease have consistently been observed among those with low socioeconomic status, and socioeconomic gradients have been observed for the CKD markers eGFR and albuminuria[4,6]. It is not fully understood what drives the association between socioeconomic status and CKD, and little has therefore been achieved in reducing socioeconomic disparities in CKD. The limited understanding of the association may in part be due to differences within and between populations, reflected by the substantial between-study heterogeneity that has been observed in meta-analysis of the association. This may be explained by differences in CKD prevalence, ethnic composition, health behavior, prevalence of risk factors, and healthcare systems[17] between populations. Therefore, country and/or population-specific estimates of the relation should be made.

Some of the observed heterogeneity may also be explained by the socioeconomic indicator that is used. In health research, socioeconomic status is commonly measured by education, income, occupational level, area/neighborhood deprivation or any combination of these[16,18-21]. The indicators are not interchangeable[18] and the choice of indicator may itself be a source of heterogeneity between studies. For example, some evidence exists that education, not income, is associated with CKD in the Netherlands, whereas in the United States, income is more strongly associated with CKD than education[22]. Educational level is sometimes the preferred indicator of socioeconomic status as it is easy to measure and yields a high response rate. It theoretically captures one's knowledge related assets and cognitive abilities. Formal education is usually completed in young adulthood and therefore reflects early life socioeconomic status[19,21]. One advantage of education as an indicator of socioeconomic status in CKD research is that, in contrast to income, it is not affected by reverse causality (i.e. disease causing low education) given that CKD usually presents at older age.

Low socioeconomic status is not likely to increase risk of CKD in a direct manner. Rather, it is proposed to affect CKD risk through a wide range of intermediate pathways, including social (neighborhood deprivation, health care affordability, health care access), psychological (e.g. depression, stress), behavioral (smoking, poor diet), and biological factors (inflammation, obesity, hypertension)[23-26]. However, these propositions are not supported by data as only one cross-sectional study formally examined the contribution of potential mediators to the socioeconomic status -CKD association in the US[27]. More study on the pathways underlying socioeconomic disparities in CKD is therefore needed. Understanding the mechanisms through which socioeconomically disadvantaged groups (e.g. those with a low educational level) show higher vulnerability to CKD may prove helpful in designing interventions to reduce socioeconomic disparities in CKD. Given the challenges of intervening on education itself, managing and/or modifying downstream effects of low education to prevent CKD in disadvantaged groups, may be a more promising approach.

Genetic underpinnings of CKD

There is strong evidence for a genetic component to CKD. It tends to aggregate in families[28-31]. Furthermore, heritability of kidney function markers, estimated from family and twin studies, range between 36 and 75%, i.e. 36-75% of variance in

kidney markers can be attributed to genetic factors[32,33], although there is paucity of data from community-based samples. With advances in high-throughput measurement platforms, it became feasible to scan the entire human genome for possible leads towards causal genes. Such scans, called genome-wide association studies (GWAS), have identified a number of common variants, or single nucleotide polymorphisms (SNPs) (See **Box 1**), associated with kidney-related traits such as glomerular filtration rate, kidney function decline, urinary albumin, serum creatinine, and serum urea, in populations of European and Asian ancestry[34-42]. GWAS thus far identified >50 SNPs associated with creatinine-estimated glomerular filtration rate (eGFRcrea) in populations of European ancestry[34-37,43,44]. The phenotypic variance explained by the combined SNPs is modest (~4%); much of the genetic factors therefore remain to be found. Through advances in methodology and ever-increasing sample sizes, as well as the analysis of alternative markers of kidney function such as serum urea, it can be expected that new variants will be discovered. These new variants will explain larger amounts of phenotypic variance in the population, which may eventually lead to improved risk stratification and a deeper understanding of the mechanisms underlying CKD.

Genetics applied to social and clinical epidemiology

Although individual effects of known genetic variants associated with kidney outcomes are small, it may be possible to use the information hidden within these

Box 1. Genome-wide association studies and single nucleotide polymorphisms

Traditional linkage studies were highly successful in identifying genetic mutations underlying Mendelian diseases and traits (i.e. those with a single underlying gene). However, linkage analysis has proven ineffective for complex, polygenic traits that do not follow Mendelian inheritance patterns, such as height and blood pressure, and diseases such as diabetes. The development of high-throughput microarrays enabled researchers to scan the human genome for genetic markers associated with complex phenotypes. Such scans, known as genome-wide association studies (GWAS), typically involve the examination of millions of genetic markers called single nucleotide polymorphisms (SNPs). SNPs are variations in a single base pair, at a single location in the DNA sequence. SNPs located in the coding region of a gene may be synonymous (not affecting protein sequence) or non-synonymous (altering the amino acid sequence of protein). SNPs not in coding regions may tag causal genetic loci by association, or contribute to the disease or trait by affecting expression of genes.

variants to improve risk prediction of CKD in individuals as well as the population. For example, the effects of the 63 genetic variants associated with eGFRcrea may be aggregated into a genetic risk score, which holds promise as a reliable and accurate proxy for a genetic component to kidney function. For example, such a genetic risk score may be used to examine gene-environment interaction; recently it has been observed that higher socioeconomic status offsets genetic risk of obesity and diabetes[45,46], and it is possible that this also applies to genetic risk of CKD.

Furthermore, SNPs can be used as instrumental variables in a quasi-experimental design named Mendelian randomization[47,48]. This method exploits the random assortment and independent assignment of alleles to individuals. Analogous to a randomized clinical trial, individuals are randomly assigned to increased or decreased exposure to a risk factor based on their genotype. Due to the random assignment, confounding is minimized. Furthermore, given that the outcomes cannot influence one's genotype, reverse causation is unlikely. Therefore, under a number of assumptions, estimates of association derived from such Mendelian randomization analyses are considered causal estimates. This method is increasingly being applied to social and clinical epidemiology. For example, in recent Mendelian randomization studies, educational attainment has been implicated as a causal factor in smoking[49,50], obesity[51], and coronary heart disease[52]. These studies lend further support for a causal role of socioeconomic factors in disease risk. Given the large body of observational evidence on the socioeconomic status - CKD association, and that many of the underlying risk factors of coronary heart disease are similar to those of CKD, it is likely there is a causal role of socioeconomic factors in CKD risk as well.

Thesis outline

Aims

In this thesis, I aim to elucidate pathways leading to CKD in the general population. More specifically, in applying concepts from genetic epidemiology to social epidemiology, I hope to increase our understanding of socioeconomic disparities in CKD risk.

Research question 1

Is educational level associated with long-term risk of CKD in the general population? If so, what are mediators of this association? (**Chapter 2**)

Research question 2

Is low heart rate variability, an indicator of poor autonomic function, associated with increased risk of CKD in the general population? (**Chapter 3**)

Research question 3

CKD is observed to aggregate in families. What are the odds of developing CKD when a family member has CKD? What is the contribution of genetic factors to the CKD defining traits, eGFR and albuminuria, in the general population? (**Chapter 4**)

Research question 4

GWAS identified 53 SNPs associated with eGFRcrea. Is a genetic risk score based on these SNPs an accurate genetic proxy of kidney function? If so, can such a genetic risk score be used for CKD risk prediction? (**Chapter 5**)

Research question 5

Serum urea is an alternative marker of kidney function. Which are the genes that influence serum urea? What function do these genes have? Can we, through these genes, gain insights into the physiology of serum urea and kidney function, and into the pathways leading to kidney disease? (**Chapter 6**)

Research question 6

Does lower education amplify the negative consequences of a higher genetic predisposition to CKD? (**Chapter 7**)

Research question 7

Can we obtain *causal* estimates of the inverse association between education and CKD using genetic proxies of educational attainment? (**Chapter 8**)

To address the research questions in this thesis, we leverage data from large samples of the general population. The two most important are the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) Study and the Lifelines cohort study and Biobank. Furthermore, we apply summary data from large GWAS consortia such as the Chronic Kidney Disease Genetics (CKDGen) Consortium, and the Social Science and Genetics Association Consortium (SSGAC). Information on data sources and study design, by thesis chapter, is provided in **Table 2**. Details on these sources are described in the referred chapter.

Thesis structure

A general introduction of this thesis is provided in **Chapter 1**. Here, concepts, constructs, and hypotheses underlying this thesis are discussed, and an overview of the available literature is provided. In **Chapter 2**, socioeconomic disparities, assessed by educational level, in long-term risk of CKD are examined. Furthermore, I explore potential underlying mechanisms of this association. In **Chapter 3**, I investigate the association of heart rate variability (HRV), a marker of poor autonomic function, with CKD. In **Chapter 4**, I construct a genetic risk score comprised of genetic variants associated with creatinine-estimated glomerular filtration rate. I then examine its cross-sectional and longitudinal associations with a number of complementary kidney outcomes to ascertain whether it is an accurate and clinically applicable representation of the genetics underlying kidney function. In **Chapter 5**, I describe a meta-analysis of GWAS to identify genetic variants associated with urea, an alternative marker of kidney function, in populations of European ancestry. In follow-up analyses, we attempt to characterize these variants and their relevance to urea physiology and kidney function and disease. In **Chapter 6**, I examine the familial aggregation of CKD, and estimate the relative contribution of genetic factors in CKD related traits. In **Chapter 7**, I address the question whether high socioeconomic status offsets genetic predisposition to reduced kidney function by examining the statistical interactions between education and a genetic risk score. In **Chapter 8**, I perform a Mendelian Randomization study to obtain causal estimates of the relation between education and kidney outcomes. Finally, in **Chapter 9**, I discuss the most important findings and their implications for clinical practice, research practice, and public health.

Table 2. Overview of thesis chapters: data sources, design, number of participants, determinants, and outcomes

Chapter		Data source(s)	Design	N	Determinants	Main outcome	Secondary outcome(s)
1	**General introduction**	-	-	-	-	-	-
2	**Educational level and risk of chronic kidney disease: longitudinal data from the PREVEND Study**	PREVEND	Cohort study	6,078	Educational level	CKD	eGFR
3	**Heart rate variability and its association with chronic kidney disease: results from the PREVEND Study**	PREVEND	Cohort study	4,605	Heart rate variability	CKD	eGFR
4	**Familial aggregation of chronic kidney disease and heritability of related biomarkers in the general population: The Lifelines Cohort Study**	Lifelines	Family study	155,936	-	CKD	eGFR, albuminuria, serum urea, uric acid, serum electrolytes
5	**Evaluation of a genetic risk score based on creatinine estimated glomerular filtration rate and its association with kidney outcomes**	PREVEND	Cohort study	3,649	Genetic risk score based on 53 eGFRcrea SNPs	CKD	eGFR albuminuria
6	**Genome-wide scan of serum urea in European populations identifies two novel loci**	Lifelines PREVEND NESDA EGCUT I+II	Two-stage genome-wide association study	20,391	Hypothesis-free: >2.5 x10^6 SNPs	serum urea	eGFR
7	**Interaction of educational level and genetic factors in kidney function**	PREVEND	Cohort study	3,597	Educational level, Genetic risk score based on 63 eGFRcrea SNPs	eGFR	-
8	**Causal effects of educational attainment on kidney outcomes: a Mendelian Randomization study**	SSGAC CKDGen Lifelines	Two-sample Mendelian Randomization study	>10^6	1271 SNPs for years of schooling	eGFR albuminuria	-
9	**General discussion**	-	-	-	-	-	-

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PART I

Evaluating the effect of socioeconomic status and autonomic dysfunction on risk of chronic kidney disease