Epidemiology of chronic kidney disease in Europe

Brück, K.

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CHAPTER 9:

Summary

SUMMARY

Background

Across European countries there is a substantial variation in the incidence of patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). The incidence of RRT is determined by the number of patients reaching ESRD, the access to, and take up rate of RRT. To date, it is unclear which factors explain the variation in RRT incidence between countries. A possible explanation is a difference in the number of patients with chronic kidney disease (CKD) progressing to ESRD.

Differences in the prevalence of CKD and/or outcomes of patients with CKD may be responsible for differences in the incidence of ESRD, and thereby contribute to the observed differences in the incidence of RRT. Therefore the aim of this thesis was to investigate if differences in the prevalence of CKD and outcomes in patients with CKD exist across European regions. In the first part of this thesis we present research on the prevalence of CKD and in the second part we present research focused on outcomes of patients with CKD.

Chapter 1 is the introduction of this thesis in which we discuss the background literature and introduce the overall aim of the thesis.

The first part of the thesis which is focused on the prevalence of CKD starts with **Chapter 2**. In this chapter we present a systematic literature review. The aim of this review was to identify all papers which report the prevalence of CKD in the European general population and to evaluate the methodology and reporting of these papers. We noticed great heterogeneity in the methodology of both the population selection and in the renal function assessment. Moreover, the assessment of the methodology was often complicated by unclear or incomplete reporting. We also observed heterogeneity in the reporting of the prevalence of CKD across papers. For example, in publications with the main focus on the prevalence of CKD, only 35% reported the 95% confidence interval (95CI%) of the CKD prevalence estimate. Moreover, only 25% standardized the CKD prevalence estimate to a national or European age distribution. Due to the heterogeneity in both methodology and reporting, we were unable to use the published prevalence estimates to compare the prevalence of CKD across countries. Therefore we formulated recommendations to improve reporting of both study methodology and CKD prevalence estimates with the aim of enhancing comparability of results from future papers.

In **Chapter 3** we contacted the studies identified in Chapter 2 to request information on the prevalence of CKD and population characteristics. Our aim was to describe the prevalence of CKD across European countries and regions. We used a uniform definition for the prevalence of CKD and standardized the prevalence estimate to the European age and sex distribution to enable cross country comparison, independent of national age and sex distributions. In addition, we presented CKD prevalence stratified by age and presence of diabetes mellitus, hypertension and obesity. Despite these standardizations we observed great variation in the prevalence of CKD across European general population studies, ranging from 3.31% (95%CI 3.30% to 3.33%) in Norway to 17.3% (95%CI, 16.5% to 18.1%) in North East Germany. A likely explanation for this variation in the prevalence of CKD is the heterogeneity of the population selection methods and renal function assessments. Another potential explanation lies in regional differences in factors associated with CKD, such as human and environmental factors, e.g. lifestyle factors, public health policies and genetic factors. Unfortunately we were unable to ascertain to what extent the reported CKD prevalence variation was caused by heterogeneity in the study methodology and to what extent by 'true' regional differences.

In **Chapter 4** we describe by means of a narrative review the implementation of public health measures related to the prevalence and complications of CKD. We focused on key CKD risk factors namely, three life style factors i.e. physical inactivity, dietary salt intake, smoking and two non-communicable diseases, diabetes mellitus and hypertension. These risk factors were chosen as they were part of the 2013 WHO action plan for the prevention and control of non-communicable diseases. All three lifestyle factors were targeted in implemented measures and appeared to be associated with health improvements in the general population. However, we were unable to find evidence suggesting that these risk factors had a beneficial effect on hard renal outcomes, such as the need for RRT. With regard to diabetes mellitus and hypertension, increased prescription rates of both glycaemic control and antihypertensive medication were described. Yet, we were unable to find papers that reported on the impact of either the prevalence of CKD or on complications of CKD.

In part 2 of this thesis we presented research on outcomes of CKD. Patients with CKD are at increased risk of developing cardiovascular disease and have a greater risk of all-cause mortality. Furthermore, renal function in patients with CKD can progressively decline, which may result in ESRD. Importantly, the vast majority of CKD patients die before ever reaching ESRD. Consequently it is important when describing outcomes in patients with CKD, to include both changes in renal function (eGFR) and mortality risk.

In **Chapter 5** we performed a systematic literature review to evaluate the influence of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement on the design and reporting of observational cohort studies. We first identified all papers from CKD cohort studies including older patients which reported mortality as an outcome. In all of the identified papers we assessed the reporting according to the 22 items of the STROBE checklist and then compared this reporting in papers published before and after

the STROBE statement publication in 2007. Although we found a slight improvement in the reporting of four STROBE items, we did not identify any improvement in the study design.

In **Chapter 6** we describe outcomes of patients with CKD followed in outpatient nephrology clinics across nine study cohorts. For each cohort we assessed both the CKD progression, measured as decline in eGFR, and all-cause mortality. Through use of a relatively new statistical technique, the joint model, we simultaneously analysed decline in eGFR and mortality risk which resulted in a mean decline in eGFR adjusted for mortality risk and a mortality risk adjusted for the decline in eGFR. Another advantage of this joint model is its ability to adjust for the measurement error in eGFR. Using this joint model with additional adjustments for age, sex, baseline eGFR and albuminuria, primary renal disease, presence of diabetes mellitus, hypertension, obesity and smoking, we observed only a small variation in the decline in eGFR across cohorts. The lowest decline in eGFR was seen in cohorts were access to nephrology specialist care was freely available. In contrast, the mortality risk varied remarkably across cohorts. We propose that it is likely that differences in population health may contribute to the observed differences in CKD outcomes, as this has been shown to explain part of the variation in mortality of patients on RRT.

In **Chapter 7**, we investigated if obesity measures are associated with left ventricular mass (LVM) in a hypertensive CKD cohort. We observed a cross sectional association between body mass index (BMI) and waist circumference (WC) in patients with early stages of CKD, which was absent in patients with more advanced CKD stages. In addition, we found that changes in BMI and WC were associated with changes in LVM in all CKD patients. These results suggest that maintaining a healthy weight may prevent the development of left ventricular hypertension in patients with CKD and thereby reduce cardiovascular risk.

In **Chapter 8,** we summarize the main results of the previous chapters and discuss the findings and possible implications. One of the main messages is that the study methodology, both through population selection and laboratory measurements, may directly influence study results such as the prevalence of CKD. Another core message is the importance of comparability of study populations and reporting of results when comparing results across studies and countries.

We started this thesis with the argumentation that differences in the prevalence of CKD and/or outcomes in patients with CKD may lead to a variation in the number of patients with ESRD and thereby contribute to the observed variation in the incidence of RRT across countries. At the end of this thesis we cannot conclude that this premise has been proven, but we have been able to show that, in contrast to prior assumptions, there is a variation in both the prevalence of CKD and in outcomes of patients with CKD across European

countries and regions. What remains for future studies is to determine to what extent the reported variations are reflecting true regional differences and if these contribute to the observed variation in the incidence of RRT.