Epidemiology of chronic kidney disease in Europe

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CHAPTER 8:

Discussion

DISCUSSION

The aim of this thesis was to determine if differences in the prevalence of CKD and in outcomes of patients with CKD exist between European regions and countries. We established the European CKD Burden Consortium to enable cross country comparison to investigate if differences in the prevalence of CKD and/or in outcomes of patients with CKD contribute to the observed variation in the incidence of RRT for ESRD (1). The results of this collaborative international network are presented in both parts of this thesis. In part 1, we investigated the prevalence of CKD in the general population and factors which influence this. In part 2 we focused on progression of CKD and other outcomes in patients with established CKD. In this chapter we will summarize and elaborate on the findings of the previous chapters. This discussion ends with an overall conclusion and a discussion of future perspectives.

CKD PREVALENCE

In **Chapter 2** we presented a study on behalf of the European CKD Burden Consortium. We performed a systematic review to identify all published papers which reported the CKD prevalence in the European general population. Although many studies reported the prevalence of CKD, results could not be directly compared due to methodological differences in both population selection and renal function assessment. The population selection showed great heterogeneity in both the methods used to identify (i.e. sampling frame) and recruit (i.e. sampling design) the study populations. This finding is important as it has been previously shown that the chosen sampling frame and sampling design may influence the representativeness of the study population (2). If the study population is healthier than the target population this may lead to an underestimation of the prevalence of CKD. Furthermore the type of renal function measurement can directly influence the prevalence of CKD, as different creatinine assays can lead to different results (3). Importantly, many papers provided insufficient information to evaluate the influence of the population selection and renal assessment method, which hinders comparison with results from other publications.

Another finding was the variety in reporting of CKD prevalence. For instance, only 25% of the studies reported an age and sex standardized prevalence estimate of which only one study standardized to the European population. As CKD is strongly associated with age, this lack of standardization will directly increase or decrease the CKD prevalence in studies with old or young participants, respectively. Reporting age and sex standardized CKD prevalence estimates, e.g. to the European population, enables comparison of CKD prevalence across studies and countries independent of the regional age and sex distribution.

Individual CKD prevalence estimates require context to enable interpretation regarding the magnitude or importance of the estimate. This context can be achieved by comparing

prevalence estimates across studies and is needed to facilitate discussions and decisions regarding public health policy and health care planning. Hence we formulated specific recommendations to improve comparability of CKD prevalence across studies through 1) clear reporting of the methodology and 2) standardized reporting of results.

In **Chapter 3** we estimated the prevalence of CKD in the adult population across 19 general population based studies from 13 countries. We contacted the investigators of all studies, identified in Chapter 2, and asked them to send us information on the prevalence of CKD and on population characteristics. All participating studies were included in the European CKD Burden Consortium. To enhance comparability of CKD prevalence across regions, we used a single definition for CKD and age and sex standardization to the EU27 population (4). In addition, we stratified CKD prevalence based on the presence of important CKD risk factors: hypertension, diabetes mellitus and obesity (5). Despite this, we found great variation in the prevalence of CKD across European regions. This variation continued across low and high risk populations, suggesting that the variation in the prevalence of CKD is at least in part independent of regional differences in the prevalence of these risk factors.

One likely explanation for the observed variation is the remaining heterogeneity in methodology of both population selection and renal function assessment. 74% of the studies used the Jaffe assay, which reportedly overestimates serum creatinine (6) and thus CKD prevalence. Fortunately 68% of studies used IDMS calibration which reduces measurement bias and improves inter-laboratory comparability (7). The influence of the population selection method on the CKD prevalence estimate is less clear, as it may both lead to an over- or underestimation of the true CKD prevalence. Importantly, the non-response analysis performed by five individual studies indicated that study populations were of equal or better health as compared to the target population (8-12), implying that the prevalence of CKD may have been underestimated in these studies. It is unlikely that all regional variation is explained by the heterogeneity in methodology, as this would require that by pure chance over- and underestimation would only occur in the countries with observed high and low CKD prevalence estimates, respectively. The remaining 'true' variation, however large or small, can possibly be explained by a regional variation in genetic factors, human and environmental factors and health care systems. Unfortunately, for now it is impossible to determine to what extent the observed variation is explained by methodological factors and to what extent by these other 'true' factors.

In **Chapter 4** we performed a narrative literature review in which we described the translation of research to public health measures influencing CKD. We focused on the implementation and effect of public health measures on the prevalence of CKD and on complications of CKD and specifically looked at measures targeting five important CKD risk factors; physical inactivity (13), high dietary salt intake (14), smoking (15), diabetes and

hypertension (5). We found that for all three lifestyle factors public health measures have been implemented which have seemingly improved population health. In contrast, there was scarce evidence on the effect of lifestyle measures on renal outcomes and none on hard outcomes such as the need for RRT. Nonetheless, these promising results suggest that public health measures may actually improve population health which may result in a reduced CKD prevalence and possibly improved CKD outcomes.

With regard to the influence of diabetes and hypertension, we found increased prescription rates for both glycaemic control and antihypertensive medication, suggesting improved treatment. Even so, several studies reported poor blood pressure control in CKD patients. Although the increased prescription rates are encouraging, we were unable to find studies reporting the impact on the prevalence of CKD and on the outcomes of patients with CKD.

CKD PROGRESSION AND OUTCOMES

As discussed in part 1 adequate reporting of study design and results is required to enable comparison of study results. Moreover, standardized reporting is beneficial to evaluate the strengths and limitations of observational studies. In 2007, the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement was published to improve reporting and eventually the design of observational cohort studies (16). In **Chapter 5** we investigated if the publication of the STROBE statement had influenced the quality of reporting and design of CKD cohort studies. For this purpose we performed a systematic review to identify all observational cohort studies reporting on mortality in older patients with CKD. In the period between 2002 and 2014, 37 papers were published, of which 26 were published after the STROBE statement was published. Although we found a marginal improvement in the reporting of four STROBE items, there was no apparent improvement in study design after the publication of the STROBE statement. However, the conclusions regarding the study design were based on what the authors reported and hence may have failed to detect unreported improvements in study design. We therefore conclude that there is still room for improvement in the standardized reporting and possibly study design of observational CKD cohort studies.

In **Chapter 6** we describe eGFR decline and mortality in patients with CKD attending outpatient nephrology clinics in Europe. After performing a literature review, we asked the authors of eligible CKD cohort studies to provide a limited dataset including individual data on baseline characteristics and repeated renal function measurements. The nine participating studies were included in the European CKD Burden Consortium. Through use of a sophisticated statistical method, we combined a repeated measures model with a survival model to calculate both annual eGFR decline and the relative mortality risk for nine CKD

cohorts. These so called joint models comprise a relatively new statistical method which adequately handles incomplete and time dependent data and adjusts for the measurement error in time varying variables (17), in our case eGFR. In addition, these joint models correct for the association between change in eGFR and mortality risk, thus providing a less biased estimate of the mean decline in eGFR and mortality hazard ratio (17). After adjustment for age, sex, baseline eGFR and proteinuria, comorbidity and smoking, we observed clinically relevant variation in CKD outcomes across the included CKD cohorts. The annual decline in eGFR was relatively slow and similar across cohorts, with the slowest eGFR decline seen in the Belgium Ghent cohort. The highest variation was found in mortality risk, with a hazard ratio (HR) ranging from 0.22 (95%CI 0.11-0.42) in the English LACKABO cohort to 1.28 (95%CI 1.11-1.48) in the English CRISIS cohort. Part of this variation may be explained through a selection of healthier patients in some cohorts which used additional exclusion criteria. Notwithstanding, the variation in outcomes persisted across cohorts with identical exclusion criteria. Therefore, we hypothesize that the observed variation in adjusted outcomes of CKD may be explained by the regional population health and healthcare system factors. Interestingly, the type of access to specialist care (gatekeeper system vs open access system) was reflected in both the rate of decline in eGFR and in the mortality risk, being lowest in cohorts with open access systems. This confirms that referral by a general practitioner does indeed filter out healthier individuals. The finding of a slower eGFR decline and lower mortality risk in open access system raises the question if some of these CKD patients would not be better treated in a primary care setting instead of in the more expensive specialist care setting. However, as we described outcomes of patients with CKD attending outpatient nephrology clinics we cannot rule out the positive effect of the management by the nephrologist. To establish if these patients are equally well off in primary care, ideally one would need a study in which the treatment of these patients is randomly allocated to primary care and specialist care.

As seen in **Chapter 6**, more patients with CKD died rather than progressing to ESRD requiring RRT. We did not distinguish between the cause of death, yet previous studies have shown that cardiovascular mortality is the most frequent cause of death in CKD patients (5). CKD is recognized as an independent risk factor for both cardiovascular disease and mortality (5) and this risk is amplified by common CKD comorbidities such as hypertension, obesity and left ventricular hypertrophy (LVH) (18). Interestingly, reduction in left ventricular mass (LVM) has been previously linked to a reduced cardiovascular risk (19, 20). As obesity is strongly associated with both CKD (21) and cardiovascular disease (22), we investigated the association between obesity measures and LVM in a hypertensive CKD cohort in **Chapter 7**. We found that within the cross sectional analyses, both body mass index (BMI) and waist circumference (WC) were associated with LVM in CKD stages 1-3, in contrast this association was not seen in more severe CKD stages. However, we

additionally studied the longitudinal association and found that, in all CKD stages, an increase in BMI and WC was associated with an increase in LVM, suggesting that prevention of obesity may independently reduce the risk of LVH and the associated risk of cardiovascular disease.

METHODOLOGICAL ISSUES

Two chapters in this thesis focus solely on methodology and the reporting of study results, indicating the importance we designate to methodology especially for the interpretation of results from observational studies. We will discuss the impact of some important methodological factors on the results of this thesis.

In well-designed general population studies the representativeness and thus generalizability is mainly influenced by the response of the population. As soon as the response is below 100% there is the possibility of non-response bias (2, 23). Importantly, non-response bias only occurs when non responders differ from responders with regard to the outcome of interest. Problematically, non-response bias can both falsely increase and decrease the outcome (2, 23). Non-response analysis may provide insight into the direction of non-response bias (23). In Chapter 3, five studies had performed non-response analysis suggesting that the study populations had similar or better health compared to non-responders.

In the CKD cohorts from Chapter 6 another type of selection bias, through use of inclusion and exclusion criteria, may have influenced the results. In chapter 6, five out of the nine CKD cohorts used additional exclusion criteria to select their study populations. The exclusion criteria used were associated with prognosis and as such may have resulted in a selection of healthier patients than generally seen in outpatient nephrology clinics. This may have led to an underestimation of both the decline in eGFR and the mortality risk. By only including patients with CKD attending outpatient nephrology clinics the generalizability of the findings is limited. Hence the progression of CKD and mortality rate observed in chapter 6, cannot be extrapolated to undiagnosed patients or to CKD patients in primary care.

Another important issue is the measurement error in serum creatinine measurements. As extensively discussed in Chapter 2 and 3, creatinine measurements are prone to both random and systematic error. Consequently the eGFR obtained through calculations from serum creatinine is also susceptible to bias. We tried to reduce the influence of this by using IDMS based creatinine results, as IDMS calibration has been proven to improve comparability (7). Still the magnitude of the variation in CKD prevalence remains unclear, as we cannot ascertain the impact of the inter-laboratory variation in creatinine results. In Chapter 6, we investigated CKD progression using repeated measurements of eGFR to

calculate change in eGFR. The advantage of this is that the influence of the systematic measurement error will impact both the first and consecutive measurements equally and consequently the difference between them will be unaffected by the systematic error. Yet, the change in eGFR will still be influenced by biological variability and by precision (i.e. random error) differences (3). This remaining influence of the measurement error has been reduced by the use of the joint model analysis (17, 24).

A methodological issue specific to the determination of the prevalence of CKD is the chronicity criterion. The chronicity criterion is part of the definition of CKD as proposed by KDIGO and entails the persistence of symptoms for at least three months (25). Recently, Benghanem Gharbi et al. have reported that the lack of applying the chronicity criterion can dramatically inflate CKD prevalence estimates in general population surveys (26). As we were unable to include the chronicity criterion in Chapter 3, the reported CKD prevalence estimates are likely to be an overestimation of the true prevalence of CKD. Moreover, in our systematic review in Chapter 2, we noticed that this criterion was not used in any of the papers which reported the prevalence of CKD in the general population. Indicating that this overestimation of the prevalence of CKD is a systematic problem inherent to the cross sectional nature of most population surveys.

Finally, all chapters within this thesis were based on observational studies and consequently no causative associations could be established. For instance, we could not conclude in Chapter 7 that interventions to reduce or prevent obesity will reduce LVH and associated cardiovascular disease. This would need to be tested in a randomized controlled trial (RCT), as RCTs are considered the gold standard to ascertain causal associations. However, as RCTs are very expensive and time consuming, it is sensible to first gain evidence from observational studies to increase the chance of a positive finding in an RCT. Moreover, in some situations RCTs are unethical or unfeasible. For instance, in the context of determining if geographical variation in the prevalence of CKD may explain the variation in the incidence of ESRD, it is virtually impossible to set up an RCT to test this. In this situation, well designed observational studies may be a valid alternative to inform policy makers of current clinical practice and outcomes.

CONCLUSIONS & IMPLICATIONS

The results from part 1 of this thesis suggest that the prevalence of CKD does vary across European regions. Although we acknowledge the likely influence of methodological heterogeneity, it is possible that other regional factors are contributing to the observed variation. For instance, public health measures directed at lifestyle factors may reduce the prevalence of CKD by improving the overall health of the general population.

In part 2 we showed that although the decline in eGFR was relatively slow across CKD

cohorts from out-patient nephrology clinics, substantial variation in all-cause mortality existed. As these differences persisted despite adjustments for important confounders, it is likely that other regional factors may cause the variation in outcomes of CKD. We hypothesize that regional regulations regarding access to specialist care and the health status of the regional population, possibly influenced by regional health policies, contribute significantly to the observed variation.

In conclusion, this thesis suggests that both the prevalence of CKD and outcomes of patients with CKD vary across European countries. Yet, the magnitude and cause of the variation still needs further investigation. Importantly, we did not link either the prevalence of CKD or outcomes of CKD to the incidence of RRT. This would be a next step to establish if differences in RRT incidence can be explained by the prevalence of CKD and/or the outcomes of patients with CKD. For now, we cannot conclude that the disparity in the incidence of RRT is influenced by the regional prevalence of CKD and the outcomes of patients with CKD. Nonetheless, the research presented here is a first step in investigating this association.

FUTURE STUDIES

More research is needed to determine the magnitude of the variation in the prevalence of CKD across European regions. Future studies could avoid the influence of renal function assessment by performing all creatinine measurements in a central laboratory. Obviously, such a European wide study would be very resource intensive which is perhaps not feasible in the current economic and scientific climate. Moreover, even in a pan European study it is highly improbable that the influence of non-response can be completely avoided as participation in general population studies is of voluntary nature.

In turn, the progression of patients with CKD can be reliably assessed on a regional or national level. Ideally all diagnosed CKD patients should be routinely included in a regional/national CKD registry, which would avoid the influence of selection bias. In practice it is unfeasible to follow a mean estimate of 10% of the general population and therefore registries may choose to include only patients with an eGFR below 30 ml/min/1.73m^2. Next to data on progression and outcomes of patients with CKD, such a registry should preferably record patient characteristics, data on risk factors and predictors for CKD progression as well as the treatment provided. Such regional CKD registries enable reliable investigation of CKD progression and outcomes and assessment of influence of implemented (public) health measures. Recently, some European countries/regions, e.g. Sweden (27) and the Italian Emilia Romagna province (28), have started such CKD registries in which referred CKD patients are registered.

Importantly, another much more cost effective alternative would be to use the ever

expanding amount of routinely collected clinical and laboratory data. For instance, to determine the prevalence of CKD, laboratory data could be linked to general practitioner (GP) records, to identify creatinine measurements from patients undergoing routine annual health check-ups. This approach may also lead to a selection bias, depending on the percentage of people registered with a GP and the percentage of patients participating in the routine health check. Yet, in countries with a gatekeeper health system, such as the Netherlands, all citizens are registered with a GP (29). In such countries, if only a few patients refuse to participate in a health check, arguably the selection bias would be no greater than in much more expensive and labour intensive population surveys. Moreover, if routine health checks are freely available for all adults, in 'theory' the entire population could be included in the estimation of the prevalence of CKD. Consequently, the certainty of the prevalence estimation would improve significantly due to the large number of subjects tested.

For assessing the progression of patients with CKD, this 'big data' approach has even more benefits. All diagnosed CKD patients can be identified and followed through laboratory databases and if these are linked to population registers and health care dataset, the natural course of renal function in patients with CKD could finally be revealed. Although this approach still has drawbacks with regard to the influence of selection bias, as diseased patients will have more frequent creatinine measurements, it is a sustainable method to evaluate change in eGFR in huge populations.

In order for this future scenario to become reality, many obstacles need to be overcome (30). The most important obstacle is the adequate handling of personal data, which is topic of ongoing societal discussion. If these privacy issues can be solved to allow data linkage on a large scale, there will be an unprecedented wealth of data to be used to optimize health care planning and further improve health care quality for all patients including patients with CKD.

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