When to start dialysis?: Clinical and methodological issues involved

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CLINICAL AND METHODOLOGICAL ISSUES INVOLVED

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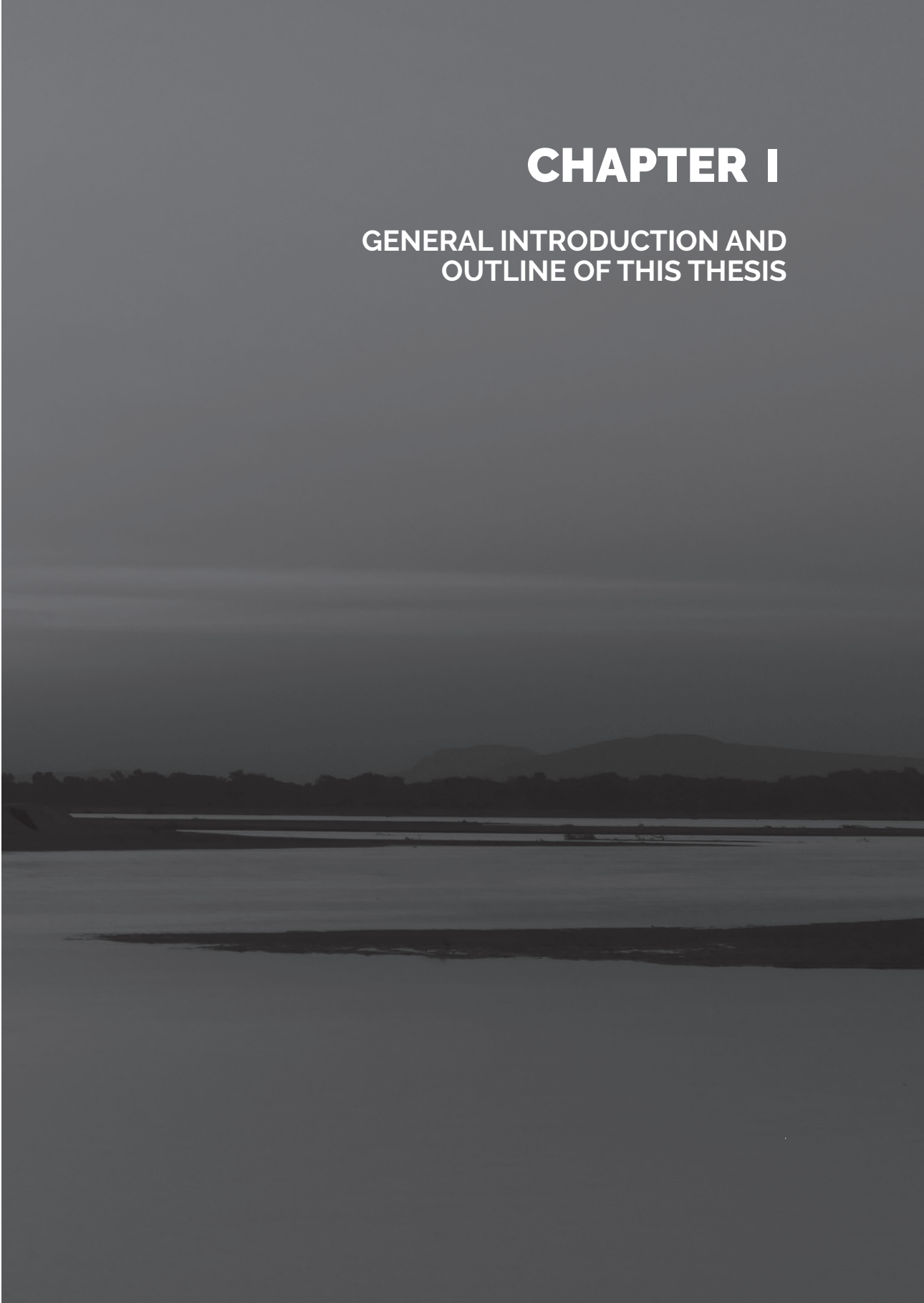
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS



Healthy kidneys maintain the fluid and mineral balance in the body, remove waste products from the blood and produce hormones, such as erythropoietin and renin.[1] In case of chronic kidney disease (CKD) there is a gradual damage of kidney structure or deterioration of function for at least 3 months with implications for health.[2] CKD is a major public health problem worldwide as the population prevalence of CKD exceeds 10%.[1]

CKD is classified based on glomerular filtration rate (GFR) and albuminuria.[2] We can distinguish five stages of CKD; the higher the stage the worse the kidney function. CKD stage 5 is also referred to as end-stage renal disease (ESRD) and in this last stage there could be need for renal replacement therapy (RRT). RRT consists of either dialysis or kidney transplantation. Dialysis and transplantation became available in the 1960s. Since then nephrologists strived to optimize RRT. Kidney transplantation is often preferable to dialysis for most patients, it results in an improved survival and a better quality of life.[3] However, not all patients are eligible for a kidney transplantation, because of comorbid conditions, or they have to wait several years until a renal allograft is available, due to limited availability of donor organs.[4] These patients rely on dialysis as RRT. The most common treatment modalities of chronic dialysis are hemodialysis and peritoneal dialysis. In hemodialysis the blood from the body is purified by an artificial kidney machine that is connected to the patient using a vascular access conduit. In peritoneal dialysis the peritoneum is used as an endogenous semi-permeable membrane to remove waste products and water excess.[5] Wastes are removed by means of a dialysate, which is transported through a catheter implanted in the abdominal cavity of a patient. After the filtering process the fluid leaves the body through the catheter and is refreshed several times a day.

Following current research guidelines for CKD patients, timely referral to specialist kidney care is recommended, that is when a patient reaches a GFR below 30 ml/min/1.73 m^2, or CKD stage 4.[2] This is also called pre-dialysis care, which aims to slow down kidney disease progression and to prepare patients for their potential start of RRT. These guidelines also state that progressive CKD should be managed in a multidisciplinary care setting, including education and counseling on different RRT modalities, dietary advice, and psychological and social care.[2]

Detailed knowledge of the rate of change in kidney function in moderate to advanced CKD patients before the start of RRT, could guide clinical decision-making and anticipate treatment choices and priorities.[6,7,8] Substantial heterogeneity exists in reported kidney function decline in CKD patients. This could relate to variations in patient characteristics between cohorts or to variability in the methodology of these studies. By design, kidney function decline could be studied prospectively in cohorts including patients with certain CKD stages, or retrospectively

in studies selecting patients based on the fact they initiated dialysis. These populations differ with regard to patient selection. In cohorts including patients with certain CKD stages, patients are followed from a similar stage in CKD progression and these patients could end up on RRT or receive no form of RRT. When patients on dialysis are selected, CKD progression is determined in a specified period prior to this dialysis initiation. As a consequence, the observed decline rates in these patients could overestimate the true underlying kidney function decline in the overall CKD population. The identification and follow-up of CKD patients at a well-defined point in the course of kidney disease progression thus seems more appropriate. As patients are included irrespective of their outcome, patient identification is not only based on patients starting dialysis, but include patients with long-term stable CKD, progressive CKD or even patients with (partial) recovery of their kidney function. Failure to select such a population potentially severely biases results of studies regarding the natural course of CKD progression.[9]

A second methodological issue that influences outcome parameters such as kidney function decline or mortality in cohort studies is the selection of incident or prevalent patients. Incident patients are new patients that could be followed from the start of a condition of interest, for instance from dialysis initiation. Prevalent patients are existing patients already having the condition of interest that could be followed from one point in time, i.e. a specific calendar date onwards. In the example of dialysis, prevalent patients would show varying dialysis vintages at cohort entry. Consequently, they are in a different disease stage at cohort entry. One might imagine that some patients are more susceptible to harm of the condition of interest and might even die prior having the chance to be included in the prevalent cohort.[10, 11] These individuals will be missing in the prevalent cohort, while this is not the case for individuals followed from the start of the condition of interest, that is, incident patients. Such cohort sampling could influence the validity of a risk factor study. It is therefore important to gain insight into how results in the nephrology research field are influenced by the type of patients selected and consider these differences prior to study setup.

Besides the type of patients selected in which for instance CKD progression is studied, it is also important how CKD progression is subsequently analyzed. To provide insight into this kidney function trajectory or CKD progression, patients are typically followed over time and their kidney function is estimated at several time points. Some patients may drop out earlier during follow-up than others and for different reasons. Furthermore, patients could show a different level of kidney function at study entry or differ in the rate of kidney function decline. In addition, the number of available kidney function estimates may vary widely between patients. This heterogeneity with respect to kidney function and dropout is important to take

into account when estimating kidney function trajectories. In general two methods are used in literature to estimate kidney function trajectories over time: linear regression to estimate individual slopes and linear mixed-effects models (LMMs), i.e. repeated measures analysis. Notably, abovementioned heterogeneity is not properly taken into account using linear regression. In contrast, in LMMs all information and variability in the data is retained. However, the underlying concepts, use and interpretation of LMMs are not always straightforward.

Besides the above-mentioned methodological issues related to scientific studies on CKD progression prior to RRT, there are also numerous clinical issues unresolved. For instance, the possible relationship between CKD progression and symptoms remains unknown in patients with advanced CKD. Patients with CKD suffer from a wide range of symptoms.[12, 13] In previous literature, it has been shown that CKD symptom burden is negatively correlated with health-related quality of life, and positively correlated with increased morbidity and mortality rates.[14, 15] Although symptom burden increases with morbidity, no specific time point demarcates the onset of symptoms in patients with progressive loss of kidney function.[16] The interplay between kidney function and symptoms is still unclear, and especially the coherence between change in kidney function and symptoms is unknown. The few studies published on kidney function and symptoms are mostly limited by their cross-sectional design.[17-19] Therefore, research into the association between kidney function decline and symptom development in a longitudinal setting remains an undiscovered area.

In addition to the possible relationship between kidney function deterioration and symptom development, the identification of modifiable risk factors for CKD progression is important for preventive or treatment strategies.[20, 21] Well-known risk factors include hypertension and diabetes mellitus.[1] Also, high phosphate levels have been consistently associated with CKD progression, as well as FGF-23 excess and the calcium-phosphorus product.[22-26] Less evidence exists on the association between disturbances in serum levels of calcium and kidney function decline. Conflicting results are reported, where some found no association between serum calcium and CKD progression, and others reported that low serum calcium was associated with a faster kidney function decline.[25, 27] These studies did not differentiate between CKD stages. Instead of pooling all patients with CKD stage 3 to 5, it is important to study the effect of such risk factors in separate CKD stages to gain insight into possible different effects among stages.

Knowledge of CKD progression in a broader sense, including methodological and clinical issues, is important to anticipate when or not to initiate dialysis. However, the optimal moment of

dialysis initiation in patients with advanced CKD is still unclear. Dialysis should not be started too early because of the burden of the dialysis therapy itself. On the other hand, we should not withheld therapy for too long in order to prevent serious complications related to ESRD itself. Clinical guidelines describe that dialysis is usually started at a kidney function of 5-10 ml/min/1.73m^2.[28] Thus far, the only randomized trial on this topic that has been performed in CKD patients is the IDEAL study.[29] No clear difference was obtained in survival rates between early and late dialysis initiation. In addition, previous observational studies showed conflicting results, either favoring later or earlier start of dialysis, and were also subjected to lead-time bias and immortal time bias, two issues arising from counting survival from dialysis initiation. First, a direct comparison between early and late starters will introduce lead-time bias. A potential survival benefit observed in early starters compared to a later-starting comparative group, could be only due to the fact that survival time is counted from an earlier moment in time in the former patients.[30]

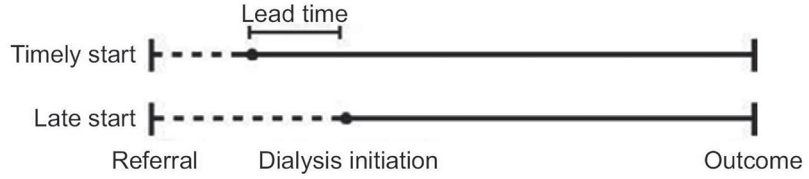


Figure 1 Lead time based on moment of referral and time of dialysis initiation.
Lead-time bias tends to favor earlier dialysis initiation, because patients starting dialysis with more residual kidney function enter dialysis earlier in the course of the disease than those starting dialysis with less residual function, and accordingly gain a spurious residual lifetime advantage. Analyzing survival from the moment of referral solves the problem of lead-time bias, as would analyzing from the moment a certain glomerular filtration rate is reached (e.g. 20 mL/min/1.73 m^2).[30]

The second issue involves that only people will be included who survive until they actually start dialysis, causing immortal time bias. Both issues can be solved by conducting a randomized trial.[29] Because survival time is then counted from a common starting point (e.g. a certain GFR) and people are classified based on the treatment strategy they are assigned to prior to dialysis initiation. Importantly, to determine the optimal starting moment of dialysis a randomized trial including many different treatment arms would be required to include all possible starting moments. Conducting an RCT may thus be unfeasible because of the patient number needed to sufficiently power all comparisons. Therefore we have to rely on observational study data. Considering these methodological and clinical issues, it is important to account for them in our question to find the optimal timing of dialysis initiation. For this purpose, more insight is needed into the impact of lead-time bias and how we can get rid of lead-time bias and immortal time bias by emulating a randomized trial using observational data.

OBJECTIVE AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide more insight into clinical and methodological issues to keep in mind when aiming to find the optimal moment for dialysis initiation in patients with moderate to advanced CKD. For this purpose we focused on methodological issues like in which type of cohort and patients CKD progression should be studied and what the best method is for analyzing kidney function trajectories. Subsequently, clinical issues like kidney function trajectories and risk factors for CKD progression are important to study for guiding clinical decision-making and anticipating treatment choices. In addition, it is important to know the impact of methodological issues involved to be able to find an optimal moment to initiate dialysis, including lead-time bias and immortal time bias.

In **chapter 2** we determined the decline of kidney function in patients with CKD stages 3-5 by performing a systematic review and meta-analysis. We highlighted the importance of the identification and follow-up of CKD patients at a well-defined point in the course of kidney disease progression. When having such a cohort, in general patients could be assembled in two ways, so called prevalent and incident cohort. In **chapter 3** we discussed the impact and considerations of using prevalent versus incident dialysis patients when investigating different risk factors in association to mortality. Besides the type of patients selected in which for instance CKD progression is studied, it is also important how the CKD progression is subsequently analyzed. For estimating the kidney function trajectories over time two approaches are generally applied: linear regression to estimate individual slopes and LMMs. In **chapter 4** we highlight important differences between these approaches. We illustrated this using a clinical example and offer a framework how to model and interpret the LMM. This methodology is subsequently used in chapters 5 and 6.

Symptom burden increases with higher morbidity and could logically increase with deterioration of kidney function, although to our knowledge this association has never been investigated in a longitudinal setting. In **chapter 5**, the association between kidney function decline and the symptom development in non-dialysis patients was investigated. Also, insight into modifiable risk factors is essential to anticipate treatment choices. In **chapter 6** we focused on the association between baseline serum calcium and subsequent rate of kidney function decline in separate CKD stages 3 to 5.

After having addressed the methodological and clinical issues during pre-dialysis, which are important to anticipate treatment choices and the fact that we rely on observational studies for finding the optimal moment to initiate dialysis, we focused on investigating the role of lead-time bias in this matter in **chapter 7**. Second, we performed a pilot study to investigate the suitability of emulating a randomized trial using observational study data to deal with both lead-time bias and immortal time bias in **chapter 8**. Finally, in **chapter 9** the results of this thesis, their implications and future research directions are discussed in the context of finding the optimal moment to initiate dialysis.

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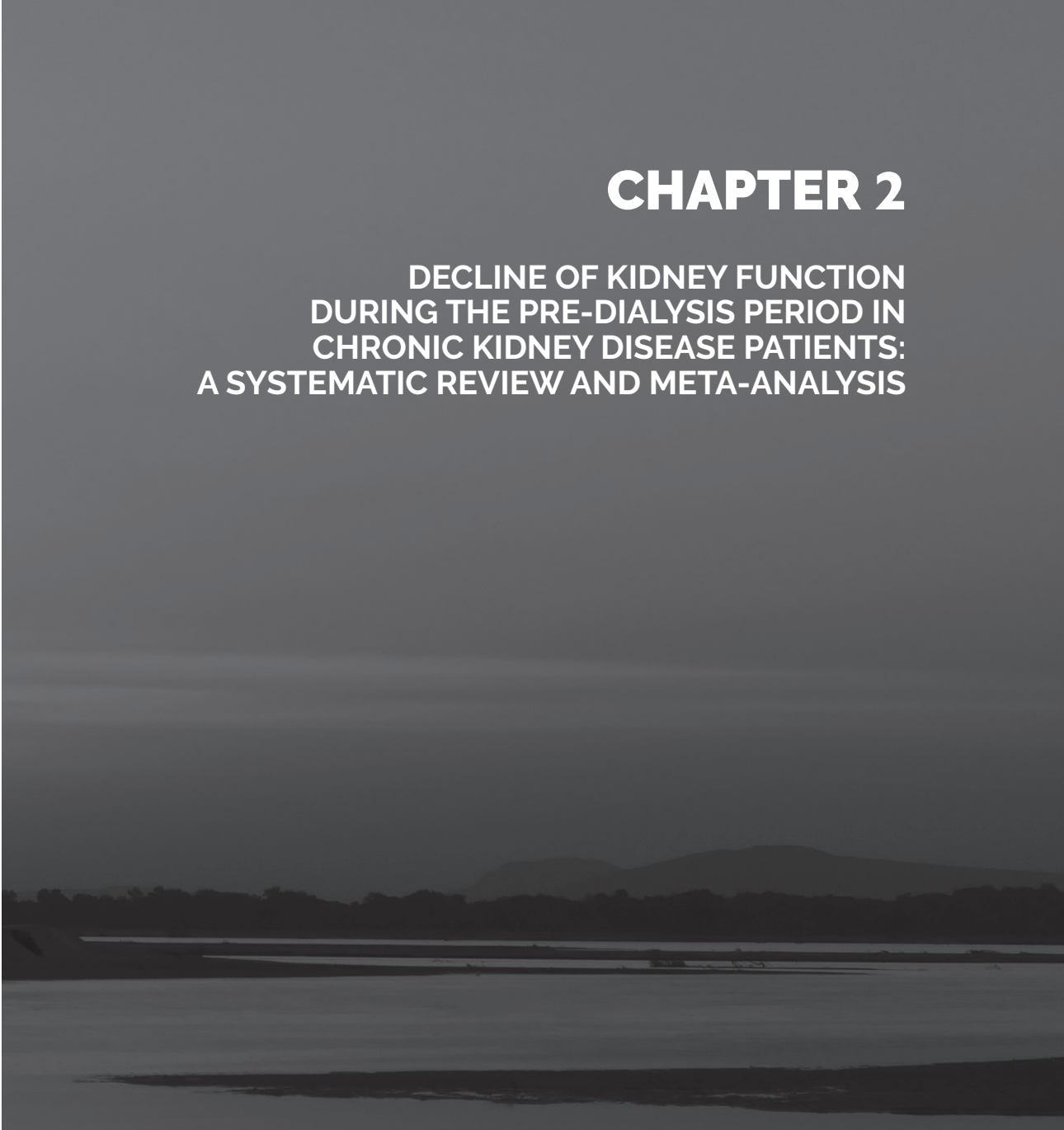
CHAPTER 2

DECLINE OF KIDNEY FUNCTION DURING THE PRE-DIALYSIS PERIOD IN CHRONIC KIDNEY DISEASE PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS



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ABSTRACT

Purpose: Substantial heterogeneity exists in reported kidney function decline in pre-dialysis chronic kidney disease (CKD). By design, kidney function decline can be studied in CKD 3-5 cohorts or dialysis-based studies. In the latter, patients are selected based on the fact they initiated dialysis, possibly leading to an overestimation of the true underlying kidney function decline in the pre-dialysis period. We performed a systematic review and meta-analysis, to compare the kidney function decline during pre-dialysis in CKD stage 3-5 patients, in these two different study types.

Patients and methods: We searched PubMed, EMBASE, Web of Science and Cochrane to identify eligible studies reporting an estimated glomerular filtration rate (eGFR) decline (mL/min/1.73m^2) in adult pre-dialysis CKD patients. Random-effects meta-analysis was performed to obtain weighted mean annual eGFR declines.

Results: We included 60 studies (43 CKD 3-5 cohorts and 17 dialysis-based studies). The meta-analysis yielded a weighted annual mean (95%-confidence interval [95%-CI]) eGFR decline during pre-dialysis of 2.4 (2.2, 2.6) mL/min/1.73m^2 in CKD 3-5 cohorts compared to 8.5 (6.8, 10.1) in dialysis-based studies (difference 6.0 [4.8, 7.2]).

Conclusions: To conclude, dialysis-based studies report faster mean annual eGFR decline during pre-dialysis than CKD 3-5 cohorts. Thus, eGFR decline data from CKD 3-5 cohorts should be used to guide clinical decision-making in CKD patients and for power calculations in randomized controlled trials with CKD progression during pre-dialysis as the outcome.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem worldwide with poor clinical outcomes.[1] Prevalence and incidence of CKD are increasing rapidly, and the demand for pre-dialysis care is growing.[2] Pre-dialysis care aims to slow down decline in kidney function and to prepare patients for their potential start of renal replacement therapy (RRT; dialysis and kidney transplantation). Detailed knowledge of the rate of kidney function decline in moderate to advanced CKD patients before the start of RRT, could guide clinical decision-making and anticipate treatment choices and priorities.[3,4,5]

Studies among CKD patients point to substantial heterogeneity in kidney function decline during the pre-dialysis period.[3,6-12] The estimated glomerular filtration rate (eGFR) is commonly used as measure for renal insufficiency in CKD patients during the pre-dialysis period. Kidney function decline during the pre-dialysis trajectory can be studied in CKD 3-5 cohorts, or in a subgroup of patients who initiated dialysis at some point, dialysis-based studies (Figure S1).[3, 11-19] These populations differ with regard to patient selection. In CKD 3-5 cohorts, patients are followed from a certain point in the pre-dialysis phase and an overall eGFR decline is reported, while not all patients end up on RRT. When patients on dialysis are selected (dialysis-based studies), eGFR decline is determined in a specified period prior to this dialysis initiation. As a consequence, we hypothesize that decline rates obtained from dialysis-based studies overestimate the true underlying kidney function decline in the overall pre-dialysis CKD population (see Supplementary Material 1 for a more detailed theoretical explanation).

A comprehensive characterization of the actual magnitude of annual kidney function decline during the pre-dialysis period is essential for clinical decision making in the management of CKD patients, including the anticipation of dialysis onset. It is also important for power calculations of randomized controlled trials aimed to study kidney disease progression. Therefore, we aimed to perform a systematic review and meta-(regression) analysis to assess and compare kidney function decline during the pre-dialysis trajectory between CKD 3-5 cohorts and dialysis-based studies.

MATERIAL AND METHODS

Eligibility criteria

We searched for studies reporting kidney function decline in the pre-dialysis period (CKD stage 3-5 [eGFR < 60 mL/min/1.73m^2]) in adult populations. The following inclusion criteria were applied: studies which defined and reported kidney function decline as eGFR or creatinine clearance were eligible, comprising a 4-variable Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or Cockcroft-Gault formula.[20-24] In case of multiple studies describing the same study population and study outcome, the study with the most complete data was selected. Only studies comprising a population of 50 patients or more were included. Meeting abstracts, case-reports, editorials and animal studies were excluded. Also, articles in other languages than English, French, German, Dutch or Spanish were not eligible.

Search strategy

We searched in PubMed, EMBASE, Web of Science and the Cochrane Database for eligible literature published between January 2000 and December 2016 (both published and epubs published in advance, Supplementary material 2). Furthermore, references of key articles were searched to identify potentially relevant studies. The systematic review was conducted according to the PRISMA guidelines.[25]

Data extraction

Studies retrieved from the search strategy were entered into reference manager software (EndNote X7) and were screened on title and abstract. Potentially relevant studies were retrieved for detailed assessment. For eligible studies, data were independently extracted by two reviewers (CJJ and CCEH). Disagreements between reviewers were resolved by consensus, or by a third reviewer (OMD) in case of remaining doubt.

For all included studies, the following data were extracted and entered into an electronic database: first author and year of publication, number of participants and population studied, setting (e.g., referral center/name of study and country), mean age, proportion male and diabetes, kidney function measure (e.g., MDRD, CKD-EPI, Cockcroft-Gault formula), duration of pre-dialysis period, mean baseline eGFR and unadjusted rates of estimated annual kidney function decline (mL/min/1.73 m^2).

For CKD 3-5 cohorts, we extracted data on the number/proportion of patients lost to follow-up and the proportion/number of patients that started dialysis or died before the end of the study. When CKD 3-5 cohorts reported both an overall kidney function decline rate during the pre-dialysis period and a separate kidney function decline for patients starting dialysis, the overall decline of the CKD 3-5 cohort was extracted. In case no patient in the CKD 3-5 cohorts reached dialysis/RRT, these cohorts were excluded and the length of follow-up during the pre-dialysis period was considered to be too short.

For dialysis-based studies, we also extracted data on the value of kidney function at the moment of dialysis initiation. For these studies loss to follow up was not applicable. Noteworthy, the unit of eGFR values is reported as mL/min/1.73m^2, which is correct using the MDRD or CKD-EPI equation. However, the Cockcroft-Gault formula estimates the creatinine clearance and is expressed in mL/min, without correction for body surface area. The creatinine clearance exceeds the GFR, because creatinine is also secreted by the proximal tubule as well as filtered by the glomerulus. For the sake of readability, we have chosen to report all eGFR and creatinine clearance values as mL/min/1.73m^2 for consistency, and because only a few studies reported the creatinine clearance values based on the Cockcroft-Gault formula.

Risk of bias assessment

Risk of bias assessment focused on design elements that could potentially bias the assessment of kidney function decline in CKD patients during the pre-dialysis period:

1. Adequacy of measurement of kidney function decline. The CKD-EPI and MDRD equation were considered adequate methods for measurement of eGFR. The Cockcroft-Gault formula was considered high risk of bias.[23, 26]
2. A proportion of loss to follow-up <10% was considered low risk of bias (CKD 3-5 cohorts).
3. Selection of patients: Inclusion of consecutive CKD 3-5 or dialysis patients was considered adequate. As an alternative, a random sample of all CKD 3-5 or dialysis patients was also considered adequate.

Elements of risk of bias assessment and potential differences of these elements between studies were used to explore potential between-study heterogeneity. Studies with low risk of bias assessment for all elements were rated as low risk of bias overall. Because only two of these three elements applied to dialysis-based studies, risk of bias assessment was repeated for CKD 3-5 cohorts using only these two selection criteria.

Statistical analysis

The main outcome of the present meta-analysis was the weighted annual eGFR decline. Results were presented separately for CKD 3-5 cohorts and dialysis-based studies. When a monthly kidney function decline was reported, the decline rate was multiplied by 12 to estimate the annual decline rate. For papers presenting results as median with interquartile range, we recalculated this to the accompanying mean with standard deviation (SD).[27, 28] Furthermore, in case a paper provided separate kidney function declines for subgroups and no decline rate for the whole study population, we calculated a weighted mean with a pooled SD in a fixed-effect model.[28] For included studies reporting no kidney function decline, the kidney function values (including variance) at start and end of follow-up/at dialysis initiation were used to estimate an annual mean decline rate with pooled SD.

Meta-analysis was performed using the DerSimonian and Laird method.[29] Given the expected clinical heterogeneity, a random-effects model was performed to take the between-study variation into account and no fixed-effects analysis was performed (unless <5 studies presented data for a specific outcome). Between-study heterogeneity was estimated using the I^2 statistic.[28] For risk of bias assessment, a meta-analysis was also performed for subgroups according to risk of bias status for both CKD 3-5 cohorts and dialysis-based studies.

Several pre-planned univariate random-effects meta-regression analyses were performed. First, the annual eGFR decline from CKD 3-5 cohorts and dialysis-based studies were compared. Sources of heterogeneity for different reported mean annual eGFR declines were identified in CKD 3-5 cohorts, as these studies better reflect an inception cohort (see Supplementary material 1). We investigated the association between the mean eGFR decline and the proportion of patients with diabetes in the study population, as diabetes is known to increase kidney function decline.[30] Furthermore, we investigated the association between the mean eGFR decline and the proportion of males in the study population, given the existing paradox that CKD 3-5 is more prevalent among women, although women are less likely to start dialysis.[31] Another important source of heterogeneity might be non-linear kidney function decline over time.[3, 32-34] To test whether the linearity assumption was violated, we performed univariate random-effects meta-regression analysis between the annual eGFR decline and two explanatory variables: duration of pre-dialysis period and mean baseline eGFR of the study population. If either of these associations were significant, this could be explained by a violation of the linearity assumption. To investigate the presence of potential publication bias, we assessed the association between study size and magnitude of reported eGFR declines by investigating the presence of funnel plot asymmetry, using Egger's test.[35]

Several sensitivity analyses were performed to validate the robustness of the results: Since random-effects models fitted by the DerSimonian and Laird method could negatively bias the between-study variance, meta-analysis was also fitted by restricted maximum likelihood (REML).[29, 36, 37] Furthermore, in CKD 3-5 cohorts, a stratified meta-analysis according to CKD stages, based on the mean baseline eGFR of each cohort, was performed. We did not perform subgroup analyses to assess whether or not the slope of decline in eGFR and creatinine clearance was different between the 3 formulas (*ie* MDRD *vs* CKD-EPI and Cockcroft Gault *vs* MDRD and CKD-EPI) or primary kidney disease, due to small subgroups or lack of information. Statistical analyses were performed with Stata Statistical Software 14.0 (Stata Corp LP, College Station, TX, USA).

RESULTS

Search results

We identified 1231 unique publications by searching PubMed, EMBASE, Cochrane Database, Web of Science and by screening reference lists of included articles (n=60). After exclusion of 1143 publications by screening of title and abstract, 88 publications were retrieved for detailed assessment, of which 60 fulfilled the inclusion criteria. To avoid multiple inclusions of the same study participants and the same study outcome, we excluded 10 publications originating from the same study populations (Supplementary material 3) and included the publication with the most complete data. Of the 60 included publications, 43 studies presented data based on CKD 3-5 cohorts and 17 studies presented data based on dialysis-based studies (Figure 1).

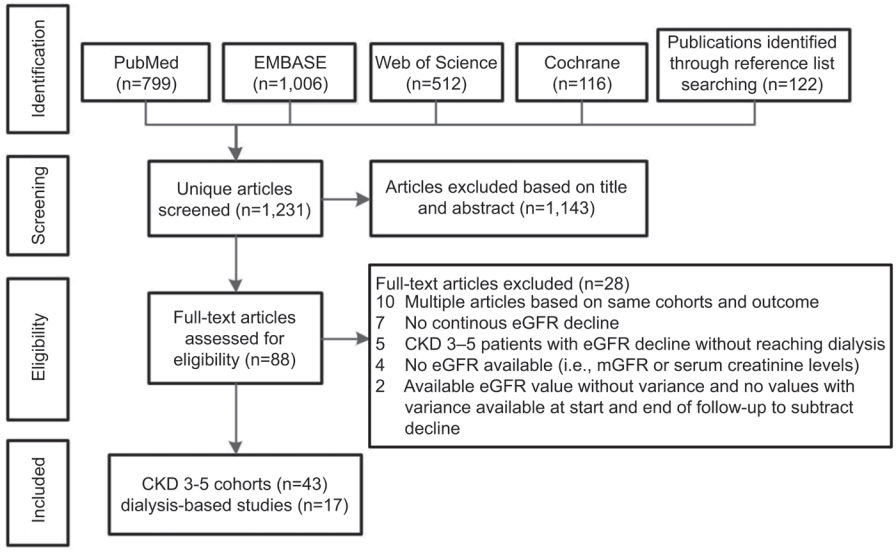

Figure 1 Flow chart for study selection of publications on kidney function decline during the pre-dialysis period in CKD 3-5 cohorts and dialysis-based studies.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; mGFR, measured GFR.

Study characteristics

Study characteristics of the 60 included studies are summarized in Table 1. In most studies the kidney function measure during the pre-dialysis period was based on a MDRD equation (31 CKD 3-5 cohorts and 10 dialysis-based studies). In total, only six studies used the CKD-EPI equation and three studies used the Cockcroft-Gault equation. In CKD 3-5 cohorts, mean pre-dialysis follow-up period ranged from 0.4 to 8.2 years and mean baseline eGFR was between 10 and 45 mL/min/1.73m^2. Individual study characteristics of included studies are shown in Table S1 and S2.

Table 1 Characteristics of included CKD 3-5 cohorts and dialysis-based studies

Characteristic	CKD 3-5 cohorts (n=43)	Dialysis-based studies (n=17)
Total participants	67 668	35 282
Participants per study (range)	62-26 246	63-18 874
Year of publication (range)	2004-2016	2001-2016
Mean age (range)	42-73[a]	56-69
% male (range)	42-97	53-98
% diabetes (range)	0-100[b]	20-100[c]
Kidney function measure		
CKD-EPI	4	2
MDRD	31	10
Cockcroft Gault	2	1
Other	6[d]	4
Mean follow-up period until dialysis initiation or end of follow-up (years, range)	0.4-8.2[e]	0.2-4.1[f]
Mean baseline eGFR (ml/min/1.73m^2, range)	10-45[g]	6-35[h]

Notes: Data are presented as number or range. [a] One study did not report mean age, but median without variance. [b] Six studies did not report % diabetes. [c] Four studies did not report % diabetes. [d] In two studies, the used eGFR measure was unclear, is counted as kidney function measure of the "other" category. [e] For 15 studies, mean follow-up period was unclear (7 reported median, 6 only planned follow-up period, in 2 studies follow-up period not available for patients included in meta-analysis). [f] For seven studies, mean follow-up period was unclear. [g] For two studies, mean baseline eGFR was unclear. [h] For seven studies, mean baseline eGFR was unclear.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, chronic kidney disease; epidemiology collaboration; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

Risk of bias assessment

The risk of bias assessment is summarized in Table S3. Only three studies used the Cockcroft-Gault formula (two of the CKD 3-5 cohorts and one of the dialysis-based studies). In CKD 3-5 cohorts, the percentage loss to follow-up ranged from 1% to 41%. Twelve studies had a loss to follow-up of <10% (low risk of bias), and nine studies had a loss to follow-up of > 10%; in most studies the percentage loss to follow-up was unclear. For 19 CKD 3-5 cohorts and 10 dialysis-based studies, consecutive or random patient sampling was applied. However, the sampling method was unclear for most studies.

Annual eGFR decline in CKD 3-5 versus dialysis-based studies

In a random-effects meta-analysis the weighted mean annual eGFR decline was 2.4 (95%-CI: 2.2, 2.6, I^2 99.1%) and 8.5 (95%-CI: 6.8, 10.1, I^2 99.8%) mL/min/1.73m^2 in CKD 3-5 cohorts and dialysis-based studies, respectively (Figure 2).

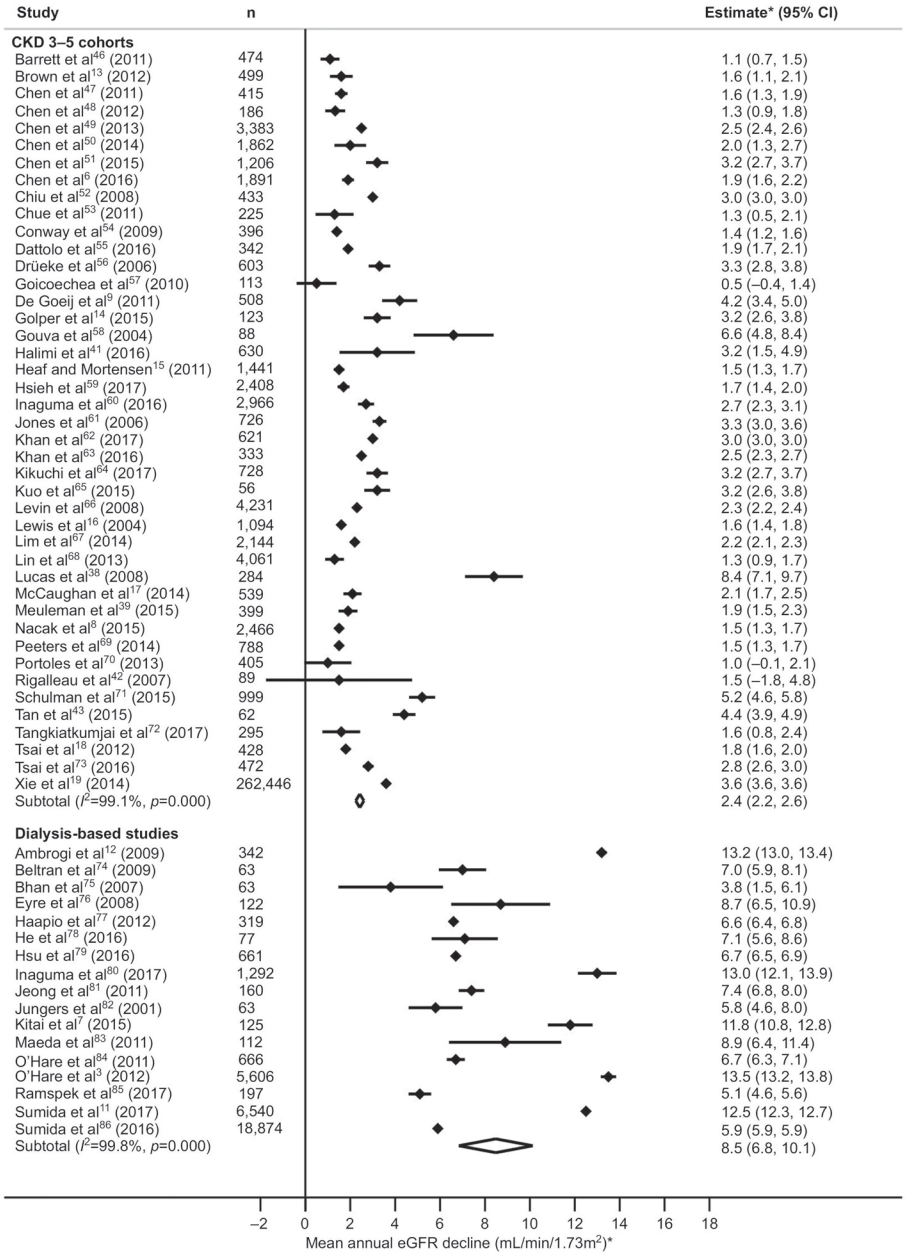

Figure 2 Random-effects meta-analyses of weighted annual eGFR declined during the pre-dialysis period based on CKD 3-5 cohorts or dialysis-based studies.
Notes: Weights are from random effects analysis. Higher values denote higher decline rate
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Identification of sources of heterogeneity using meta-regression analysis

Univariate meta-regression analysis showed a large difference in kidney function decline between CKD 3-5 cohorts versus dialysis-based studies: difference 5.99 mL/min/1.73m^2/year (95%-CI: 4.80, 7.19). Important is to identify which cohort characteristics are associated with a faster mean annual kidney function decline, such as the proportion of diabetes or males in the study population. The mean annual eGFR decline and the proportion of diabetes in CKD 3-5 cohorts were not significantly associated in meta-regression analysis (per 10%, β=0.06 mL/min/1.73m^2, 95%-CI: -0.14, 0.27, Figure S2A). We should note here that there was one outlier with a reported mean annual kidney function decline of 8.4 (±11.1) mL/min/1.73m^2 and only 9.2% of the population had diabetes.[38] After exclusion of this outlier, the meta-regression analysis yielded a significant association between annual eGFR decline and the proportion of participants with diabetes in CKD 3-5 cohorts (β=0.18 mL/min/1.73m^2, 95%-CI: 0.04, 0.33, Supplemental Figure 2b). This equates to a 0.18 mL/min/1.73m^2 increase in weighted mean annual eGFR decline for every 10% increase in the proportion of participants with diabetes. The mean annual eGFR decline and the proportion of males in CKD 3-5 cohorts was not significantly associated in meta-regression (per 10%, β=0.12 mL/min/1.73m^2, 95%-CI: -0.36, 0.60). Meta-regression analysis showed that the mean annual eGFR decline in the pre-dialysis period was not clearly associated with duration of the pre-dialysis period (difference=0.19 mL/min/1.73m^2, 95%-CI: -0.09, 0.48), nor with the mean baseline eGFR value (difference=0.01 mL/min/1.73m^2, 95%-CI: -0.06, 0.05) in CKD 3-5 cohorts. We found an association between study size and magnitude of reported mean annual eGFR declines for CKD 3-5 cohorts (Egger's test p-value=0.002) and no clear association for dialysis-based studies (Egger's test p-value=0.11, see Figure S3 for funnel plots).

Sensitivity and subgroup analysis

For CKD 3-5 cohorts, 6 studies were assessed as low risk of bias and 37 as high risk of bias, with a weighted mean annual eGFR decline of 2.6 (95%-CI 2.0, 3.2) and 2.4 (2.2, 2.7) mL/min/1.73m^2, respectively. For dialysis-based studies, 7 studies were assessed as low risk of bias and 10 as high risk of bias, with a weighted mean (95%-CI) annual eGFR decline of 8.2 (6.5, 9.9) and 8.7 (6.8, 10.1) mL/min/1.73m^2, respectively. Risk of bias assessment was repeated for CKD 3-5 cohorts using the two selection criteria applied to dialysis-based studies. This yielded similar weighted mean annual eGFR declines of 2.6 (95%CI: 2.3, 3.0) and 2.4 (2.0, 2.6) mL/min/1.73m^2 for studies with low risk and high risk of bias, respectively. In subgroup analysis for CKD stage 3a, 3b, 4 and 5, decline rates were 1.7 (three cohorts; 95%-CI: 1.4, 2.1), 2.4 (17

cohorts; 95%-CI: 2.0, 2.7), 2.5 (21 cohorts; 95%-CI: 2.2, 2.8), and 3.0 (two cohorts; 95%-CI: 0.8, 5.3) mL/min/1.73m^2, respectively. In a random-effects meta-analysis using linear mixed models fitted with restricted maximum likelihood, similar results were obtained.

DISCUSSION

This meta-analysis showed that the reported mean annual eGFR decline during the pre-dialysis period is larger in patients from dialysis-based studies compared to CKD 3-5 cohorts. We found that the weighted mean annual eGFR decline was 8.5 (95%-CI: 6.8, 10.1) in dialysis-based studies compared to 2.4 (95%-CI: 2.2, 2.6) mL/min/1.73m^2 in CKD 3-5 cohorts. Importantly, CKD 3-5 cohorts are more likely to represent the true eGFR decline prior to dialysis, given the way dialysis-based studies select their patients. These results underline that eGFR decline estimations from CKD 3-5 cohorts, as opposed to dialysis-based studies, should be used for clinical decision-making in CKD 3-5 patients, such as in the context of anticipating treatment decisions and priorities, for instance, the moment to start dialysis. These eGFR decline estimations from CKD 3-5 cohorts should also be used for power calculations in randomized controlled trials with kidney disease progression in pre-dialysis CKD patients as primary outcome.

To our knowledge, this is the first meta-analysis directly comparing the annual eGFR decline in CKD 3-5 cohorts and dialysis-based studies. A number of previous CKD 3-5 cohorts reported both an overall eGFR decline and an eGFR decline for patients who initiated dialysis, as in dialysis-based studies. In these studies the reported annual eGFR decline for the whole CKD population ranged between 1.5 and 2.1 mL/min/1.73m^2, and for patients who initiated dialysis between 3.9 and 7.3 mL/min/1.73m^2.[15, 17, 18] Previous literature is in line with our finding that the mean annual rates of kidney function decline in CKD 3-5 cohorts are much lower than in dialysis-based studies.

CKD 3-5 cohorts comply with the definition of an inception cohort, in which patients are included from a well-defined point in the course of the kidney disease progression, irrespective of their outcome. However, in dialysis-based studies patients are selected on their outcome, i.e. dialysis start, providing biased estimates of kidney function decline in CKD 3-5 patients (for more in-depth explanation of the inception cohort, Supplementary material 1). An intuitive interpretation is that some patients in CKD 3-5 cohorts will only progress very slowly, or even stay stable for such a long period that they will never initiate dialysis. Such patients are not included in dialysis-based studies. This is also shown empirically in The Netherlands: during

the first years on pre-dialysis care, 45-64% of CKD 4-5 patients start dialysis therapy; 1-8% of these patients receive a kidney transplant as first form of RRT and 5-7% dies without receiving any form of RRT.[9, 10, 39, 40]

We should acknowledge substantial study diversity was present in our meta-analysis. We used different methods to identify sources of heterogeneity, including differences in risk of bias, publication bias or heterogeneity due to study diversity. Risk of bias assessment showed that the mean annual eGFR declines did not materially differ between studies with a low risk of bias compared to those with a high risk of bias, for both CKD 3-5 cohorts and dialysis-based studies.

Surprisingly, we did not find a strong association between the proportion of diabetes and the mean annual eGFR decline in our meta-analysis. This could be due to one outlier, with only 9.2% of diabetics in the CKD population and a mean annual rate of kidney function decline of 8.4 (±SD 11.1) mL/min/1.73m^2.[38] This high annual eGFR decline could be explained by the fact that the study population comprised human immunodeficiency virus-positive patients and was mostly of African-American origin. Both human immunodeficiency virus and African-American descent are well-known risk factors for a greater annual eGFR decline.[30] After exclusion of this outlier, the association became significant, in line with our current understanding of the association between diabetes and kidney function. Of note, in our meta-analysis, three CKD 3-5 cohorts comprised only diabetic CKD 3-5 patients, showing mean annual eGFR declines of 1.5, 3.2 and 4.4 mL/min/1.73m^2.[41-43] It should be emphasized that a meta-analysis with study level data is not optimal to assess the association between variables such as diabetes and eGFR decline.[44]

A major strength of this study is that the mean annual eGFR decline was investigated separately and compared for CKD 3-5 cohorts and dialysis-based studies. Also, a large number of studies was included (n=60), comprising 43 CKD 3-5 cohorts and 17 dialysis-based studies. Therefore, the weighted effect estimates were not influenced largely by random error and it was possible to examine sources of heterogeneity within the CKD 3-5 cohorts.

Our study has some potential limitations. First, the outcome kidney function decline was not always reported in title or abstract, which made assessing eligibility cumbersome. Second, we assumed a linear decline in kidney function in our modeling, although it has been proposed in the nephrology literature this is not necessarily the case.[3, 19, 45] However, meta-regression techniques are known to have difficulties with correct model specification. In our meta-regression we could not show an association between either the mean duration of the pre-

dialysis period or the mean baseline eGFR value and the reported annual eGFR declines in CKD 3-5 cohorts, which suggests that the linear assumption is not violated. In other words, the reported annual eGFR decline did not significantly differ for varying durations of the pre-dialysis period or mean baseline eGFR values reported in the included cohorts. Third, publication bias is an issue of concern in all meta-analyses. In our analysis, we aimed to study the decline in eGFR, and it is difficult to predict what role publication bias could play when assessing a descriptive outcome such as eGFR. We found an association between study size and reported eGFR magnitude for CKD 3-5 cohorts, implying that publication bias could be present. However, in the funnel plot, no clear pattern is visible that studies with a smaller sample size tend to report smaller or larger annual eGFR declines than studies with a larger sample size. Finally, we did not have individual patient data.

CONCLUSION

In summary, we showed that the reported mean annual eGFR decline during the pre-dialysis period is much larger in patients from dialysis-based studies compared to that in CKD 3-5 cohorts. Importantly, implications for clinical decision-making with regard to the management of CKD patients during the pre-dialysis period and the active planning of RRT should be based on CKD 3-5 cohorts, due to the improper selection of the CKD population in dialysis-based studies.

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SUPPLEMENTARY MATERIAL

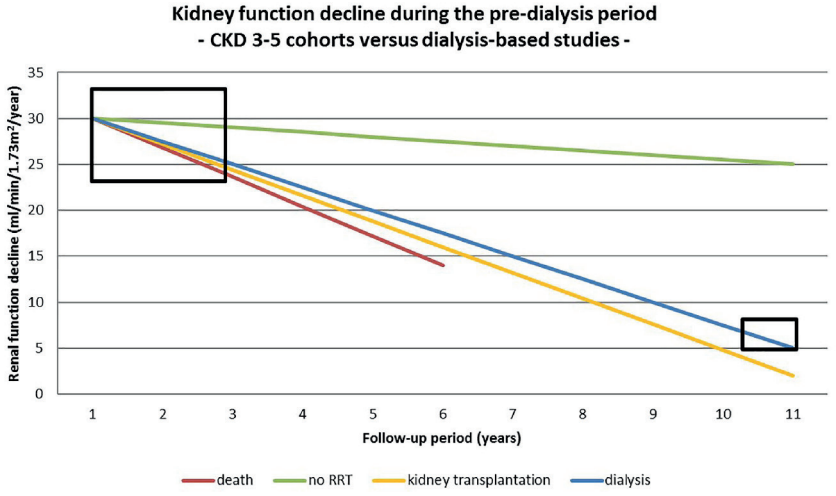

Figure S1. Graphical representation of the hypothetical difference between patients from CKD 3-5 cohorts and dialysis-based studies. In CKD 3-5 cohorts, CKD 3-5 patients are followed from a certain point in the pre-dialysis phase and only a part of the patients starts dialysis therapy. The annual eGFR decline during the pre-dialysis period is the overall decline rate for all four subgroups (green, blue, yellow and red line). However, in dialysis-based studies, patients on dialysis are selected (blue line) and their associated eGFR decline is determined in a specified period before dialysis initiation. Black boxes represent the duration of the pre-dialysis period over which the eGFR declines are reported.

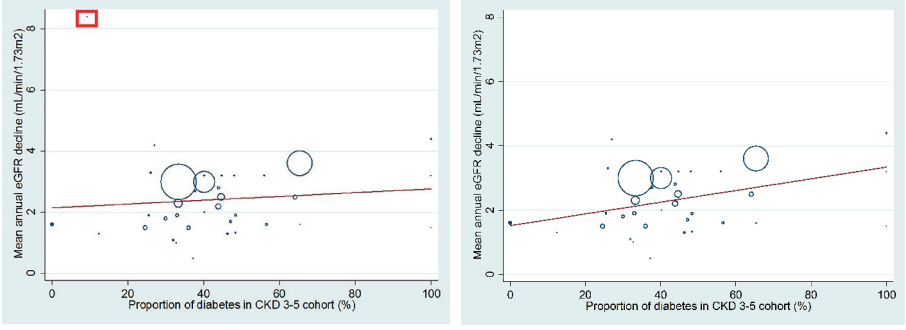

Figure S2. Meta-regression plot for proportion of diabetes and mean annual eGFR decline. At the left hand side, all CKD 3-5 cohorts. Red box represent the sole outlier reported by Lucas et al.[31] On the right hand side, all CKD3-5 cohorts except this sole outlier.

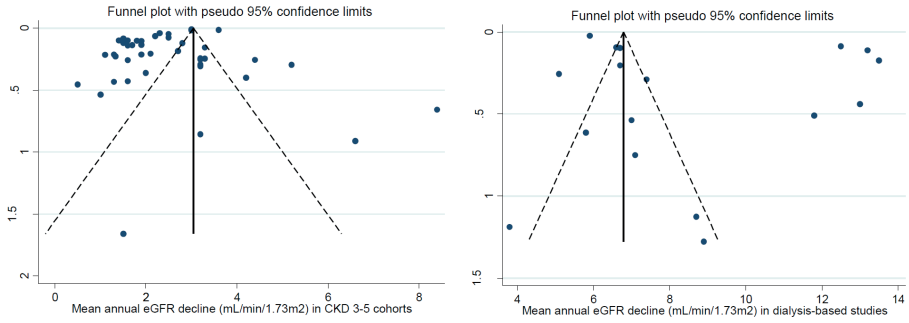

Figure S3. Association between study size and eGFR magnitude represented in funnel plots for CKD 3-5 cohorts (a) and dialysis-based studies (b).

Supplementary material 1

Inception cohort

In the current meta-analysis we distinguished between CKD 3-5 cohorts and dialysis-based studies. To clarify the difference between these study types from a methodological point of view, we elaborate on the concept of an inception cohort. An inception cohort is a group of individuals identified and assembled for subsequent study at a well-defined point in the course of the specified health condition. In this case the inception cohort requires identification of all CKD 3-5 patients and follow-up kidney function decline over time. In such an inception cohort patients are included irrespective of their outcome, thus, patients with long-term stable or even recovering kidney function are included as are those whose kidney disease progresses and start dialysis. Failure to select an inception cohort often severely biases studies on the natural history of disease, e.g. kidney disease progression.[1] It follows that dialysis-based studies do not comply with this definition and could give biased estimates of kidney function decline in CKD 3-5 patients.

[1] Porta M. *Dictionary of Epidemiology.* New York, NY: Oxford University Press, 2016

Supplementary material 2: Search strategy (PubMed, Web of Science, Cochrane, EMBASE)

PubMed

(((”pre-dialysis”[tw] OR pre-dialy*[tw] OR ”predialysis”[tw] OR predial*[tw] OR ”chronic renal”[tw] OR ”chronic kidney”[tw] OR ”Renal Insufficiency, Chronic”[Mesh] OR ”Kidney Failure, Chronic”[Mesh] OR ”end stage renal”[tw] OR ”end stage kidney”[tw] OR ”CKD”[tw] OR ”ESRD”[tw] OR ”ESKD”[tw]) AND (”Glomerular Filtration Rate”[Mesh] OR ”eGFR”[tw] OR ”GFR”[tw] OR ”glomerular filtration rate”[tw] OR ”renal function”[tw] OR ”kidney function”[tw] OR renal function*[tw] OR kidney function*[tw]) AND (”slope”[tw] OR ”slopes”[tw] OR slope*[tw] OR ”decline”[tw] OR declin*[tw] OR ”trajectory”[tw] OR ”trajectories”[tw] OR trajector*[tw] OR ”deteriorate”[tw] OR ”ascend”[tw] OR ”descend”[tw] OR ”accelerate”[tw] OR ”decelerate”[tw] OR deteriorat*[tw] OR ascend*[tw] OR descend*[tw] OR accelerat*[tw] OR decelerat*[tw] OR ”chronic kidney disease progression”[tw] OR ”ckd progression”[tw] OR ”renal progression”[tw] OR ”progression of CKD”[tw] OR ”progression of chronic kidney disease”[tw] OR ”progression of chronic renal failure”[tw] OR ”progression of renal diseases”[tw] OR ”progression of renal failure”[tw] OR ”progression of kidney disease”[tw] OR ”kidney progression”[tw] OR ”progression”[tiab] OR progress*[tiab]) AND (”Renal Dialysis”[mesh] OR ”Dialysis”[mesh] OR ”dialysis”[tw] OR ”hemodialysis”[tw] OR ”renal replacement therapy”[tw] OR ”Renal Replacement Therapy”[Mesh] OR ”Hemofiltration”[tw] OR ”Hemodiafiltration”[tw] OR ”Kidney Transplantation”[tw] OR ”Haemofiltration”[tw] OR ”Haemodiafiltration”[tw] OR ”Renal Transplantation”[tw]) AND (”initiation”[tw] OR initiat*[tw] OR ”start”[tw] OR start*[tw] OR ”commencing”[tw] OR commenc*[tw] OR ”beginning”[tw] OR begin*[tw] OR ”entering dialysis”[tw])) OR ((”pre-dialysis”[tw] OR pre-dialy*[tw] OR ”predialysis”[tw] OR predial*[tw] OR ”chronic renal”[tw] OR ”chronic kidney”[tw] OR ”Renal Insufficiency, Chronic”[Mesh] OR ”Kidney Failure, Chronic”[Mesh] OR ”end stage renal”[tw] OR ”end stage kidney”[tw]) AND (”3”[ti] OR ”4”[ti] OR ”5”[ti] OR ”three”[ti] OR ”four”[ti] OR ”five”[ti] OR ”iii”[ti] OR ”iv”[ti] OR ”v”[ti]) AND (”stage”[ti] OR ”stages”[ti] OR ”late”[ti]) AND (”Glomerular Filtration Rate”[Mesh] OR ”eGFR”[tw] OR ”GFR”[tw] OR ”glomerular filtration rate”[tw] OR ”renal function”[tw] OR ”kidney function”[tw] OR renal function*[tw] OR kidney function*[tw]) AND (”slope”[tw] OR ”slopes”[tw] OR slope*[tw] OR ”decline”[tw] OR declin*[tw] OR ”trajectory”[tw] OR ”trajectories”[tw] OR trajector*[tw] OR ”deteriorate”[tw] OR ”ascend”[tw] OR ”descend”[tw] OR ”accelerate”[tw] OR ”decelerate”[tw] OR deteriorat*[tw] OR ascend*[tw] OR descend*[tw] OR accelerat*[tw] OR decelerat*[tw] OR ”chronic kidney disease progression”[tw] OR ”ckd progression”[tw] OR ”renal progression”[tw] OR ”progression of CKD”[tw] OR ”progression of chronic kidney disease”[tw] OR ”progression of chronic renal failure”[tw] OR ”progression of renal diseases”[tw] OR ”progression of renal failure”[tw] OR ”progression of kidney disease”[tw] OR ”kidney progression”[tw] OR ”progression”[tiab] OR progress*[tiab]))) NOT (”Animals”[mesh] NOT ”Humans”[mesh]) NOT ((”Case Reports”[ptyp] OR ”case report”[ti]) NOT (”Review”[ptyp] OR ”review”[ti])) NOT (”editorial”[ptyp] OR ”comment”[ptyp]

Embase

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Web of Science

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COCHRANE

(("pre-dialysis" OR pre-dialy* OR "predialysis" OR predial* OR "chronic renal" OR "chronic kidney" OR "chronic kidney disease" OR "chronic kidney failure" OR "end stage renal" OR "end stage kidney" OR "CKD" OR "ESRD" OR "ESKD" OR "end stage renal disease") AND ("Glomerulus Filtration Rate" OR "eGFR" OR "GFR" OR "glomerular filtration rate" OR "Kidney Function" OR "renal function" OR "kidney function" OR renal function* OR kidney function*) AND ("slope" OR "slopes" OR slope* OR "decline" OR declin* OR "trajectory" OR "trajectories" OR trajector* OR "deteriorate" OR "ascend" OR "descend" OR "accelerate" OR "decelerate" OR deteriorat* OR ascend* OR descend* OR accelerat* OR decelerat* OR "chronic kidney disease progression" OR "ckd progression" OR "renal progression" OR "progression of CKD" OR "progression of chronic kidney disease" OR "progression of chronic renal failure" OR "progression of renal diseases" OR "progression of renal failure" OR "progression of kidney disease" OR "kidney progression" OR "progression" OR progress*) AND ("renal replacement therapy" OR "Dialysis" OR "dialysis" OR "hemodialysis" OR "renal replacement therapy" OR "Hemofiltration" OR "Hemodiafiltration" OR "Kidney Transplantation" OR "Kidney Transplantation" OR "Haemofiltration" OR "Haemodiafiltration" OR "Renal Transplantation") AND ("initiation" OR initiat* OR "start" OR start* OR "commencing" OR commenc* OR "beginning" OR begin* OR "entering dialysis")) OR ti/ab/kw (("pre-dialysis" OR pre-dialy* OR "predialysis" OR predial* OR "chronic renal" OR "chronic kidney" OR "chronic kidney disease" OR "chronic kidney failure" OR "end stage renal" OR "end stage kidney" OR "CKD" OR "ESRD" OR "ESKD" OR "end stage renal disease") AND ("Glomerulus Filtration Rate" OR "eGFR" OR "GFR" OR "glomerular filtration rate" OR "Kidney Function" OR "renal function" OR "kidney function" OR renal function* OR kidney function*) AND ("slope" OR "slopes" OR slope* OR "decline" OR declin* OR "trajectory" OR "trajectories" OR trajector* OR "deteriorate" OR "ascend" OR "descend" OR "accelerate" OR "decelerate" OR deteriorat* OR ascend* OR descend* OR accelerat* OR decelerat* OR "chronic kidney disease progression" OR "ckd progression" OR "renal progression" OR "progression of CKD" OR "progression of chronic kidney disease" OR "progression of chronic renal failure" OR "progression of renal diseases" OR "progression of renal failure" OR "progression of kidney disease" OR "kidney progression" OR "progression" OR progress*)) AND TI ("3" OR "4" OR "5" OR "three" OR "four" OR "five" OR "iii" OR "iv" OR "v") AND ("stage" OR "stages" OR "late")

Supplementary material 3

References of excluded full text articles, which were based on the same outcome and patient population as final included studies (n=10):

1. Chang JM, Chen SC, Huang JC, Su HM, Chen HC. Anemia and Left Ventricular Hypertrophy With Renal Function Decline and Cardiovascular Events in Chronic Kidney Disease. *American Journal of the Medical Sciences*. 2014;347(3):183-189.
2. Chen SC, Chang JM, Liu WC, et al. Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(4):724-732.
3. Chen SC, Chang JM, Tsai YC, et al. Left atrial diameter and albumin with renal outcomes in chronic kidney disease. *Int J Med Sci*. 2013;10(5):575-584.
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5. Goicoechea M, Garcia d, V, Verdalles U, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis*. 2015;65(4):543-549.
6. Liu WC, Hung CC, Chen SC, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol*. 2012;7(4):541-548.
7. Nacak H, van DM, de Goeij MC, Rotmans JI, Dekker FW. Uric acid: association with rate of renal function decline and time until start of dialysis in incident pre-dialysis patients. *BMC Nephrol*. 2014;15:91.
8. Rigalleau V, Garcia M, Lasseur C, et al. Large kidneys predict poor renal outcome in subjects with diabetes and chronic kidney disease. *BMC Nephrol*. 2010;11:3.
9. Tsai YC, Hung CC, Kuo MC, et al. Association of hsCRP, white blood cell count and ferritin with renal outcome in chronic kidney disease patients. *PLoS One*. 2012;7(12):e52775.
10. Tsai YC, Tsai JC, Chiu YW, et al. Is fluid overload more important than diabetes in renal progression in late chronic kidney disease? *PLoS One*. 2013;8(12):e82566.

Table S1. General characteristics of CKD 3-5 cohorts

First author and year of publication*	No. of participants and population studied	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Renal function equation used	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] annual eGFR decline (ml/min/1.73 m²/year)[a,b]	Number/ percentage of subjects initiated dialysis, had ESRD, died	Renal function at start of dialysis	Loss to follow-up (LTFU) (n + reason)
Barrett 2011	474 CKD 3-4 patients	compare nurse-coordinated model of care (E, n=238) and usual care (U, n=236) on achievement of treatment targets for surrogate outcomes (i.e. change in kidney function)	Five urban centers, Canada (2005)	Median 67 (IQR 61.5; 72)	E=55 female U=56 female	E=31 U=33	Re-expressed (175) 4-variable MDRD	Median 742 (IQR 614-854) days	E=Median 42 (IQR 40,46) U= median 42 (IQR 37, 46)	-1.9 (95%CI: -1.2; -2.6) over 20 months (adjusted for baseline eGFR)	N=3 dialysis (E=2, U=1) N=9 died (E=7, U=2)	N.R.	10% (20 LTFU, 27 withdrawal)
Brown 2012	499 CKD 3-5 patients	rate of CKD progression in non-obese (n=368) and obese (n=131) subjects	CRISIS, UK	Non-obese: 65 [±15] Obese: 60 [±13]	Non-obese: 61 Obese: 59	0	Original (186) 4-variable MDRD	Nonobese: 38 [±21] months Obese: 39 [±21] months	< 60 ml/min /1.73m²	Non-obese: −1.77 [±5.68] Obese: −1.28 [±6.13]	92 RRT (72 non-obese, 20 obese) 56 died (47 non-obese, 8 obese)	N.R.	<9% (44 were excluded before analysis due to withdrawal from the study, lost or insufficient data or patient discharge)
Chen 2011	415 CKD 3-5 pre-dialysis patients	association between echo-cardiographic left ventricular structural and functional parameters and progression to start	Kaohsiung Medical University Hospital, Taiwan (2007)	66.6 [±12.1]	63.9	56.6	Original (186) 4-variable MDRD	27.3 [±11.1] months	27.3 [±14.0]	-1.58 [±0.14 =SEM]	76 (18.3%) HD	N.R.	Unclear

First author and year of publication*	No. of participants and population studied	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Renal function equation used	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] annual eGFR decline (ml/min/1.73 m²/year)[a,b]	Number/percentage of subjects initiated dialysis, had ESRD, died	Renal function at start of dialysis	Loss to follow-up (LTFU) (n + reason)
		dialysis and rate of renal function decline											
Chen 2012	186 stage 3-5 CKD patients	assessing whether the combination of brachial-ankle pulse wave velocity (baPWV) and the ratio of brachial pre-ejection period (bPEP) to brachial ejection time (bET) is useful in identifying stage 3-5 CKD patients at risk for adverse renal outcomes	Regional hospital in southern Taiwan (2009)	63.4 [±12.5]	123/186 = 66.1%	Low baPWV; low bPEP/bET(n=46): 32.6 Low baPWV; high bPEP/bET (n=47): 34.0 High baPWV; low bPEP/bET (n=47): 61.7 High baPWV; High bPEP/bET (n=46): 65.2	Original (186) 4-variable MDRD	22.1 [±13.4] months	Low baPWV; low bPEP/bET (n=46): 36.5 [±19.0] Low baPWV; high bPEP/bET (n=47): 41.1 ± 13.3 High baPWV; low bPEP/bET (n=47): 33.5 ± 17.1 High baPWV; High bPEP/bET (n=46): 30.3 ± 15.6	-1.33 [±SE 0.23]	2 HD	N.R.	Unclear
Chen 2013	3393 patients with CKD stage 3-5	association of dyslipidaemia with RRT and CKD progression	ICKD study, Taiwan (2002)	63.5 [±13.5]	42.2[c]	44.6	Original (186) 4-variable MDRD	1150.3 [±577.6] days	24.7 [±15.1]	Median -2.2 (IQR -5.6; -0.1)	N=957 HD N=116 PD N=7 renal transplant N death unspecified	N.R.	Unclear (90 in the first 3 months, not further described)

First author and year of publication*	No. of participants and population studied	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Renal function equation used	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] annual eGFR decline (ml/min/1.73 m²/year)[a,b]	Number/percentage of subjects initiated dialysis, had ESRD, died	Renal function at start of dialysis	Loss to follow-up (LTFU) (n + reason)
Chen 2014	1862 ND CKD 3-5 patients	determining whether eGFR AUC% is associated with renal outcomes in progression to RRT	ICKD, Kaohsiung Medical University Hospital and Kaohsiung Municipal Hsiao-Kang Hospital, Taiwan (2002)	63.6 [±13.4]	58.2	40.2	Original (186) 4-variable MDRD	28.7 [±14.0] months	27.2 [±14.2]	-0.17 [±0.03] per month[d]	N=564 (30.3%) start RRT	N.R.	Unclear
Chen 2015	1206 CKD 3B-5 patients	evaluating the effect of a multidisciplinary (MDC, n=592) care program versus non-multidisciplinary (non-MDC, n=614) i.a. on dialysis incidence, eGFR decline [e]	National Taiwan University Hospital (2007)	MDC: 62.16 [±13.16] Non-MDC: 61.93 [±13.68]	MDC: 57.9 Non-MDC: 53.6	MDC: 44.3 Non-MDC: 45.0	Original (186) 4-variable MDRD	Median 2.43	MDC: 22.41 [±11.64] Non-MDC: 22.05 [±12.14]	MDC: -2.57 [±6.64] non-MDC: -3.74 [±10.40]	MDC: 230 (38.9%) RRT (148 (64.3%) HD, 73 (31.7%) PD, 9 (3.9%) Tx) Non-MDC: 319 (52.0%) RRT (216 (67.7%) HD, 100 (31.3%) PD, (0.9%) Tx) Death: MDC: 7.6% Non-MDC: 5.9%	MDC: 4.47 Non-MDC: 4.40	Unclear

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Chen 2016	1891 patients with baseline eGFR <45	effect of change in proteinuria (UPCR≤0.3, n=1261 and UPCR>0.3, n=630) on composite endpoint was dialysis start and renal death before	6 hospitals in nationwide multidisciplinary pre-ESRD care program, Taiwan (2008)	UPCR≤0.3: 67 [±13] UPCR>0.3: 65 [±13]	UPCR≤0.3: 59.8 UPCR>0.3: 51.1	UPCR≤0.3: 46.9 UPCR>0.3: 51.3	Original (186) 4-variable MDRD	32.0 [±12.3]	UPCR≤0.3: 25.10 [±10.54] UPCR>0.30: 20.96 [±10.24]	-1.93 [±5.89]	60 deaths (39 UPCR≤0.30; 21 UPCR>0.30) 307 dialysis (153 UPCR≤0.30;) 154 UPCR>0.30	N.R.	Unclear
Chiu 2008	433 patients with CKD stages 3-5	investigating rate and predictors of renal progression and pre-ESRD mortality in Taiwanese under nephrologists' care	National Taiwan University Hospital (2007)	65.6 [±14.1]	61.7	33.3	Original (186) 4-variable MDRD	Median 27.8 months	27.2 [±14.3]	2.99 [SE±0.20]	123 (28.4%) RRT (102 HD, 19 PD, 2 transplantation) 41 (9.5%) died	N.R.	22
Chue 2011	225 CKD 2-4 patients	investigating impact of serum phosphate, simultaneously with pulse wave velocity and augmentation index on combined end-point of start dialysis or ≥25% eGFR decline	Queen Elizabeth University Hospital, Birmingham (2004)	59 [±13]	60	12	Original (186) 4-variable MDRD	Median 924 days (IQR 637-1176)	43 [±19]	-0.11 [±0.54] per month	11 (5%) died	N.R.	Unclear

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Conway 2009	396 CKD 4 patients	Identifying factors associating mortality and commencing RRT	Health Boards, Ireland and Scotland (1998)	71.6 (median)	50.5	N.R.	eGFR[f]	Median 3.76	Mean 22.5	Median (IQR) age <65 (n=112): −2.25 (−4.2; 0.6), Age 65–74 (n=150): −1.38 (−3.2; +0.4), Age ≥75 (n=134): −0.86 (−2.3; +1.2)	89 (22.5%) RRT 180 (45.5%) died 20 (5.1%) no RRT	Mean at RRT: 8.0, 8.4, 9.8 in those aged <65 years, 65–74 and ≥75 years, resp.	10, no reason described
Dattolo 2016	342 CKD 5 patients	role of ACE-I (ACE-I n=188; no ACE-I n=154) in slowing the progression of renal damage	Santa Maria Annunziata Hospital, Florence, Italy (2002)	ACE-I: median 70 (IQR 68-73) No ACE-I: median 72 (IQR 69-75)	ACE-I: 63 No ACE-I: 62	ACE-I: 33 No ACE-I: 32	re-expressed (175) 4-variable MDRD	In months 1st-2nd quartile (Q): 17 [±19] 3rd Q: 14 [±18] 4th Q: 11 [±14] (from table 2)	ACE-I: median 10.2 (IQR 9.8-10.8) No ACE-I: median 10.1 (IQR 9.6-10.7)	ACE-I: -0.96 [±1.1] No ACE-I: -3.12 [±2.1]	201 (59%) dialysis 81 (24%) no RRT 60 (17%) died	Dialysis 10 [±4] No RRT: 12 [±5] Dead: 10 [±5]	Unclear
Drüeke 2006	603 CKD 3-4 patients	Effect of complete (group 1, n=301) versus partial correction of anemia (group 2, n=302) on cardiovascular outcomes	CREATE trial (2000)	Group 1: 59.3 [±14.6] Group 2: 58.8 [±13.7]	Group 1: 57 Group 2: 51	Group 1: 27 Group 2: 25	Cockcroft-Gault	12 months[g]	Group 1: 24.9 [±6.3] Group 2: 24.2 [±6.0] (Cockcroft Gault, decline is also based on this formula)	Group 1: 3.6 [±6.7] Group 2: 3.1 [±5.3][g]	238 dialysis (127 group 1, 111 group 3) 52 died (31 group 1; 21 death group 2)	N.R.	15% (89 withdrew (excluding those with reason of death): 27 adverse events,

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													37 withdrawal of consent or lack of co-operation, other 25 unclear)
Goicoechea 2010	113 patients with an eGFR <60	the effect of allopurinol (n=57) versus control group (n=56) in reduction of inflammatory markers and renal disease progression	Hospital General Universitario Gregorio Marañón, Spain (2007)	Allopurinol: 72.1 [±7.9] Control: 71.4 [±9.5]	N.R.	Allopurinol: 39 Control: 36	4-variable MDRD (unclear which one)	23.4 [±7.8] months	Allopurinol: 40.6 [±11.3] Control: 39.5 [±12.4]	Allopurinol: +1.3± (SE1.3) Control: -3.3± (SE 1.2) over 24 months	2 dialysis 2 deaths	N.R.	9 (6 control and 3 allopurinol), no reason specified
De Goeij 2011	508 incident CKD 4-5 patients on pre-dialysis care	association between blood pressure and CKD progression	PREPARE-1, The Netherlands (1999)	Median 63 (IQR 50-73)	57	27	Original (186) 4-variable MDRD	Median 351 (IQR 144-365) days	13.1 [±5.8]	-0.35 [±0.75] per month [b]	23% HD 22% PD 5% died	N.R.	1%, reason not specified
Golper 2015	123 patients receiving arterio-venous fistula (AVF) creation	investigating eGFR decline in progressive CKD before and after successfully created AVF	Vanderbilt Nephrology Clinic, USA (2005)	Median 68 (IQR 59.0-76.0)	59 (41 female)	56	Original (186) 4-variable MDRD	Median 638 days before AVF creation; 549 days after AVF creation	28.3 [±11.93]	Before AVF: -5.90 (95%CI: -5.28; -6.51); after AVF: -0.46 (95%CI: -1.05; 0.14)	72 HD 6 transplanted 37 no RRT 4 died	N.R.	4, no reason specified

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Gouva 2004	88 predialysis patients (SCr 2.0-6.0 mg/dl) with non-severe anemia	Whether early (n=45) compared to deferred (n=43) EPO treatment can slow down CKD progression	14 participating hospitals, Greece (2000)	Early: 66.7[±10.4] deferred: 64.2[±12.2]	Early: 25/45= 55.6 deferred: 25/43= 58.1	N.R.	Cockcroft-Gault	Median 22.5 (IQR 16-24) months	Early: 25.7 [±9.1] Deferred: 22.3 [±6.0]	At 12 months: Early: 21.9 [±9.4] deferred: 16.1 [±6.3][i]	28 RRT (10 early, 18 deferred) 7 died (3 early, 4 deferred)	Early: 11.1 [±1.5] deferred: 11.0 [±1.8]	3, no reason specified
Halimi 2016	986 DM type II patients with CKD	assessing blood pressure and proteinuria control after a 2-year follow-up	ALICE-PROTECT cohort, France (2010)	Mean 70	74	100	MDRD (not specified which)	23 [±2.4] months[i]	40 [±20.3]	at year 2: 33.9 [±20.9] [i,j]	72 dialysis, 60 died	N.R.	296 (all lost contact; 257 without complications, 39 by year two, with complications)
Heaf 2011	1441 patients with an initial eGFR < 60 and follow-up for at least 2 years	Determining rate of GFR loss in CKD population, before ESRD and influence of ACE inhibitors on it	Herlev hospital, Denmark (1986)	58.7 [±14.9]	57	N.R.	Original (186) 4-variable MDRD	5.5 [±3.8]	30.8 [±15.1]	-1.47 [±4.54]	420 (29%) ESRD	N.R.	Unclear
Hsieh 2017	2408 CKD 3-5 patients	investigating uric acid in association with all-cause mortality, CVD mortality, RRT, rapid renal progression	CKD care program, Changhua Christian Hospital, Taiwan (2001)	65.7 [±12.6]	56.9	Q1 n=605: 43.8 Q2 n=600: 44.5 Q3 n=604: 51.66 Q4 n=599: 48.58	Original (186) 4-variable MDRD	1107.2 [±789.6] days	24 [±12.9]	-1.72 [±6.7]	563 (23.3%) deaths, 652 (27%) RRT (490 HD, 162 PD)	Death: 18.3 [±12.9] RRT: 4.85 [±2.12]	Unclear

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Inaguma 2016	2966 CKD patient under nephrology care	Identifying risk factors for CKD progression to ESRD (for separate CKD stages: G3a (n=306), G3b (n=1045), G4 (n=1149), G5 (n=466)	CKD-JAC study, Japan (2007)	60.3 [±11.6]	62.1 (females 37.9)	37.7	eGFR[k]	Median 3.9	28.9 [±12.2]	G3a: -1.925 [±5.681] G3b: -2.056 [±5.924] G4: -3.182 [±14.189] G5: -3.754 [±6.374]	N.R.	N.R.	121 withdrawn, excluded, or LTFU (were excluded from original) 3087 patients
Jones 2006	726 CKD 3-5 patients [l]	Investigating decline in kidney function prior to and following nephrology referral and its association with mortality	General Hospital Southampton, UK (1997)	72 [±14]	61	N.R.	Original (186) 4-variable MDRD	pre-referral: up to 5 years post referral: Median 2.9 (IQR 1.3–4.1)	median 29 (IQR 18–38) at referral	Median (IQR) pre-referral: -5.4 (-13; -2) post referral: -0.35 (-3; 3)	178 (25%) died 73 (10%) RRT	N.R.	Unclear
Khan 2017	621 CKD 3-4 patients	investigate rate and predictors of CKD progression in NDD-CKD cohort under nephrologist care	Hospital University Sains Malaysia (2004)	61.09 [±6.57]	52.7	40.1	CKD-EPI	> 10 y	33.25 [±4.7]	-3.01 [±0.40]	113 (18%) died 270 RRT (135 of CKD stage 3; 135 CKD stage 4)[m]	N.R.	41% (430: 321 LTFU and 109 referral other healthcare center, were excluded prior analysis)

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Khan 2016	333 non dialysis CKD patients with GFR <60	assessing the role of diuretics on adverse renal outcomes	Tertiary care hospital, Malaysia	64.5 [±6.43]	57	64	CKD-EPI	1	23.7 [±7.1]	-2.5 [±1.4]	36 (11.5%) dialysis (28 HD and 8 PD) 2 death	N.R.	N=21, 9 discontinuation of diuretics
Kikuchi 2017	728 CKD 2-5 patients	association of combination of low BMI and serum albumin level with rapid CKD progression	CKD-ROUTE study, Japan (2010)	66.9 [±13.3]	70.1	40.1	eGFR[k]	<2	31.1 [±18.1]	-3.2 [±6.6]	283 (38.9%) dialysis or eGFR decrease of ≥ 30%	N.R.	26% (255 LTFU, excluded prior analysis)
Kuo 2015	56 CKD 3b-5 patients out of 149 CKD 1-5 patients [n]	If compliance index derived from digital volume pulse predicts renal function progression, i.a.	National Cheng Kung University Hospital, Taiwan (2008)	64 [±10]	79	48	CKD-EPI	51 [±12] months	30 [±10]	-3.24 [±2.16]	8 HD, 2 PD	N.R.	Unclear
Levin 2008	4231 patients with an eGFR < 30	Risk factors for rapid progression of kidney disease and death	BC CKD Registry, (2000)	66.8 [±14.5]	56	33	eGFR (unclear)	Median 31 (IQR 19-43) months	Progression ≤ 2.2 (50% of total): 22.1 [±6.1] Progression 2.3-5.0 (24% of total): 21.5 [±6.0] Progression > 5.0 (26% of total): 21.9 [±5.6]	Median -2.18 (IQR -5.14; 0.21)	1608 dialysis 71 transplanted 510 died	N.R.	unclear (1% lost to follow-up in first 2 years)

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Lewis 2004	1094 African Americans with GFR 20-65	comparison iGFR and eGFR with time to halving of GFR or doubling serum creatinine	AASK Study, US (1995)	55 [±11]	61 (39 were female)	N.R.	eGFR= 329 x $(Scr)^{-1.096}$ x$(age^{-0.294}$ x (0.736 if female)	<5	45.7 [±13.0] (from reference 10/11)	-1.64 [±SE 0.10] (overall linear slope)	88 ESRD 78 deaths	N.R.	Unclear
Lim 2014	2144 CKD 3-4 patients	investigating serum calcium as an independent prognostic marker of rapid renal function progression	Integrated CKD care program Kaohsiung Medical University Hospital, Taiwan (2002)	64.2 [±13.5]	64.7 (35.3 female)	43.8	Original (186) 4-variable MDRD	Median 1085 (IQR 682-1673) days	33.2 [±11.9]	median -1.9 (IQR -5.4; 0.5)	294 (13.7%) RRT 270 (12.6%) death	N.R.	Unclear
Lin 2013	4061 CKD 3b-5 patients	investigating changes in eGFR and risk factors of initiating dialysis	27 pre-dialysis clinics, Taiwan (2007)	70.1 [±12.3]	56.4	46.3	Original (186) 4-variable MDRD	15.0 [±10.9] months	22.4 [±11.0]	0.47 [±SE 0.42]; -1.27 [±SE 0.32]; -2.69 [±SE 0.39] for stages 3b, 4, and 5	558 (13.7%) dialysis (484 HD, 74 PD) 94 (2%) deaths	N.R.	795 (19.6%) (defined as not uploaded data > 1 year prior to end of study period)
Lucas 2008	284 prevalent or incident CKD subjects (overall cohort of n=4259)	racial differences (253 African American and 31 white) in the incidence and progression of HIV-related CKD	Johns Hopkins HIV Clinical Cohort, Maryland (1990)	White: median 46 (IQR 40-54) African: Median 41 (IQR 37-49)	White: 65 African: 60	White: 6 American: 10	Original (186) 4-variable MDRD	Mean 4.5 (mean for all 4259 patients, unclear for 284 patients)	White: Median 52 (IQR 45-56) African: Median 45 (IQR 33-53)	White: -1.5 (95%CI: -5.0; 2.0) African: -9.2 (95% CI -10.6; -7.9) *after baseline GFR adjustment	100 (35%) ESRD	N.R.	Unclear

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McCaughan 2014	539 adult recipients of first, deceased donor transplants with a functioning graft at 12 months	comparing eGFR decline rate in renal transplant recipients (with n=140; without graft failure, n=399) and between those returned to dialysis or not	Belfast City Hospital, Northern Ireland (1986)	without: 45 [±14.1] With: 40 [±14.2]	without: 62 with: 71	without: 9 with: 6	Original (186) 4-variable MDRD	Median 11 years and 9 months	Unclear	-2.1 [±4.8] (based on 464 patients)	234 dialysis (192 HD, 26 PD) 140 death	Transplant (n=134): 9.7 [±3.8] Transplant-naive (n=100): 9.1 [±2.9]	Unclear
Meuleman 2015	416 incident predialysis patients receiving specialized predialysis care	identifying illness perceptions and its association with disease progression	PREPARE-2, The Netherlands (2004)	Median 68.5 (IQR 55.7–75.6)	66.3	25.5	Original (186) 4-variable MDRD	Median 12.4 (IQR 5.3–21.9) months	16.92 (95% CI 16.28; 17.56)[o]	−1.92 (95% CI −2.35; -1.50)[n]	29 (7.0%) died 32 (7.7%) kidney transxplant 55 (13.2%) no RRT 223 (53.6%) dialysis (138 HD, 85 PD)	10.5 [±4.4]	19% (total 77: 17 recovered kidney function, 48 refused further treatment, 8 transfer other center, 4 other reason)

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Nacak 2015	2466 patients with CKD 3-5 and baseline uric acid	baseline uric acid in association with renal function decline and time to RRT	Swedish Renal Registry – Chronic Kidney Disease (SSR-CKD), Sweden (2005)	68.98 [±13.59]	65.4	36.0	re-expressed (175) 4-variable MDRD	Median 26 [IQR 16.3; 38.6]	24.95 [±9.80]	−1.48 (95% CI−1.65; −1.31)	12.6% (N=311) HD 7.1% (N=175) PD 1.8% (N=44) transplanted 26.4 (N=652) died	N.R.	Unclear
Peeters 2014	788 patients with Cockcroft-Gault 20-70 ml/min	effect of adding nurse practitioner support to physician care (intervention, n=395) versus physician care alone (control n=393) on renal endpoints	MASTERPLAN study, The Netherlands (2004)	Intervention: 58.9 [±13.1] control: 59.3 [±12.8]	Intervention: 67 control: 68	Intervention: 26 control: 23	re-expressed (175) 4-variable MDRD	Median 5.7	Intervention: 35.9 [±14.2] control: 35.2 [±12.9]	Intervention: -1.26 [±SE 0.12] Control: -1.71 [±SE 0.12]	166 RRT (77 intervention, 89 control) 105 died (50 intervention, 55 control)	N.R.	11 (from reference list), no reason specified
Portoles 2013	405 CKD 3 patients	investigate onset of anemia of renal origin and its association with the evolution of kidney disease	NADIR-3 study, Spain (2005)	67 (range 22-78)	69.9 (30.1 female)	32.8	Original (186) 4-variable MDRD	Max. 36 months	39.1 [±9.1]	End of follow-up 36.0 [±12.3] (mean 1.1 ml/min without variance) [i]	13 started RRT 26 died	N.R.	11% (43 drop-outs: 12 invest. criteria, 13 moved other hospital, 3 withdrew consent, 15 other reasons)

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Rigalleau 2007	89 patients with diabetes and eGFR <60	investigating difference in subjects with normo- (n=15), micro- (n=36) and macro-albuminuria (n=38) on CKD progression and death	Centre Hospitalier Universitaire de Bordeaux, France (2001)	64 [±11]	55.1 (Normo: 66 female Micro: 52 female macro: 29 female)	100	Original (186) 4-variable MDRD	Mean 3.2 months (calculated based on Normo: 40 [±8] Micro: 38 [±11] macro: 37 [±13] months)	All: 41.3 [± 13.1] Normo: 45.6 [±8.9] Micro: 43.8 [±12.2] macro: 37.2 [±14.5]	(measures end of follow-up) Normo: 45.8 [±8.5] Micro: 43 [±12.8] macro: 29.5 [±21.1] [i]	10 death (3 micro-, y macro-) 12 dialysis (2 micro-, 10 macro-)	N.R.	Unclear
Schulman 2015	999 ITT placebo population from 1999 non-dialysis patients with moderate to severe CKD [p]	Whether addition of AST-120 (n=1000) to standard therapy (n=999) can slow the progression of renal disease	EPPIC-1 and EPPIC-2 trial, US (2007)	55.6 [±14.6]	60.3	N.R.	eGFR (equation not specified)	N.R.	22.04 [±7.23]	Fast decliners (N=499): -10.22 [±SE 0.43] Slow decliners (n=500): -0.28 [±SE 0.26]	321 ESRD 103 death	10.44 [±4.99] (derived from table 6)	Unclear
Tan 2015	62 CKD 3-4 patients with type 2 diabetes and proteinuria	follow-up post-trial study on the association of intervention/ community care (CC, n=30) and usual care (UC, n=32) on all-cause mortality or composite renal event (ESRD)	DEFEND study, New Zealand (2004)	CC: 63 [±6.6] UC: 60 [±7.1][q]	35/65=53.8[o]	100	Original (186) 4-variable MDRD	Median (IQR) in months Original trial: 17 (11–21) Post-trial: CC: 47.5 (20.25-82.53) UC: 52 (24.5-68)	CC: 36 [±15] UC: 39 [±14]	CC: Median −3.1 (IQR −5.5, −2.3) UC: median −5.5 (IQR −7.1, −3.0)	30 dialysis or ESRD 16 died	N.R.	Unclear

First author and year of publication*	No. of participants and population studied	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Renal function equation used	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] annual eGFR decline (ml/min/1.73 m²/year)[a,b]	Number/percentage of subjects initiated dialysis, had ESRD, died	Renal function at start of dialysis	Loss to follow-up (LTFU) (n + reason)
Tangkiatkumjai 2017	339 CKD 3-5 patients [r]	association between medication adherence (low, n=62); high, n=233) and CKD progression	Chulalongkorn University & Srinakharinwirot University, Thailand (2012)	68 [±12]	48 (52 female)	65	Thai re-expressed (175) 4-variable MDRD	Median 12 (range 9-16) months	39 [±12]	Low: -4.4 [±6.7] high: -0.9 [±7.4]	18 (6%) started dialysis 28 (8%) died	N.R.	16 (5%), reason unspecified
Tsai 2012	428 CKD patients not requiring dialysis	association between depressive symptoms and progression to requirement of maintenance dialysis	Kaohsiung hospital, Southern Taiwan (2007)	57 [±15]	62 (38 female)	30	Original (186) 4-variable MDRD	25.2 [±11.9] months	Median 27 (IQR 11-48)	Median -1.6 (IQR -4.2; 0.1)	119 dialysis 17 died	Median 4.0 (IQR 3.4; 5.5)	50 (11.7%), no reason specified
Tsai 2014	472 non dialysis CKD stage 4-5 patients	association of fluid status and CKD progression	Kaohsiung hospital, Southern Taiwan (2011)	65.4 [±12.7]	54.4	43.9[s]	Original (186) 4-variable MDRD	Median 17.3 (IQR 14.0-19.1) months	15.4 [±7.5]	Median -2.0 (IQR -5.2; 0.1)	71 (15%) dialysis (65 HD; 6 PD) 0 died	N.R.	Unclear
Xie 2016	26246 patients who entered CKD stage 4	eGFR trajectories in association with kidney disease outcomes and mortality	US Veterans Affairs Healthcare system, USA (2007)	73.17 [±8.41]	97.0	65.3	CKD-EPI	Median 4.34 (IQR 1.72; 5.00)	44.63 [±17.45]	Median -3.44 (IQR -6.05; -1.65)	37% (N=9809) composite endpoint of kidney failure (eGFR <15), dialysis or transplantation. 36%- (N=14550) died	N.R.	Unclear

Abbreviations:
N.R. not reported; HD=hemodialysis; PD=peritoneal dialysis, CKD=chronic kidney disease, RRT=renal replacement therapy, ESRD=end-stage renal disease
* Published between January 2000 and December 2016 (both finally published and epubs published in advance).
[a] Indicated as mean [±SD], unless indicated otherwise.
[b] Negative values represent a faster decline rate of GFR; positive values represent slower decline rate of GFR.
[c] Derived from table 1, however in the first paragraph of the results is stated 1909/3303=58%.
[d] Decline rate is derived from table 2, but there is no unit of decline rate mentioned in the table. The method section states that the decline rate is calculated per year. However, in the example of figure 2 the unit is per month. For current meta-analysis, we assumed that the decline rate was calculated per month.
[e] Cited from the article "A total 1382 patients were enrolled, including 721 multidisciplinary care group and 661 nonmultidisciplinary care group patients. Using age, sex, chronic kidney disease stage, and diabetes mellitus status as variables, 592 multidisciplinary care recipients were matched to 614 nonmultidisciplinary care patients".
[f] $eGFR=175 \times [0.011312 \times (SCr - c)/m]^{-1.154} \times age^{-0.203}$ (× 0.742 if female); *C* and *M* are correction factors required to correct individual laboratory results to ID-MS values as determined by NEQAS.
[g] decline rate over first 12 months of follow-up, GFR decline rate is not provided over the full follow-up period.
[h] Mean decline in GFR was calculated for 436 patients, who had ≥2 eGFR measurements to estimate the kidney function decline rate.
[i] Decline rate was calculated based on mean difference between initial baseline eGFR measure and GFR measured at the end of follow-up. Standard deviations of initial baseline eGFR value(s) were pooled with SDs from GFR value(s) at the end of follow-up. The derived mean ±SD was divided by the mean follow-up time (in years) to calculate the mean annual eGFR decline.
[j] Of 986 patients, 630 patients were followed for 2 years. The mean follow-up is calculated over these 630 patients. Furthermore, the mean decline rate is 3.2 ml/min/1.73m^2 following the results, but no variance (SD or SE) is described. Therefore, we used the baseline GFR with the GFR given at year 2 to calculate the mean GFR decline with corresponding SD. The GFR value at year to is also based on these 630 patients.
[k] eGFR (ml/min/1.73 m^2) = 194 x Serum creatinine$^{-1.094}$ xAge$^{-0.287}$ x 0.739 (if female).
[l] All baseline characteristics are at moment of referral for nephrology care.
[m] Based on the sentence: "Out of 372 progressed patients, 93 (21%) patients with CKD stage 3 progressed to stage 4, 42 (10%) to non-dialysis dependent (NDD) stage 5 and 135 (31%) progressed to RRT. On the other hand, 15(8%) and 135(31%) patients with CKD stage 4 progressed to NDD stage 5 and RRT respectively." However, the total number of patients in this sentence exceeds the number of 372 progressed patients, it concerns 420 patients.
[n] The follow-up period and the number of patients that initiated dialysis were only available for all 149 patients. Other results are based on data from the 56 CKD3b-5 patients, since this is the population of interest for this meta-analysis.
[o] 399 patients had at least one kidney function (eGFR) estimation and were included for calculation of renal function decline.
[p] Based on 999 pooled placebo ITT population, no decline for AST-120 group. Other possibility of renal function at begin and end of follow-up for calculating decline not possible, because no mean follow-up known.
[q] from the complete DEFEND trial of 65 patients (ref: Hotu C *et al. Nephrol Dial Transplant* 2010; **25**: 3260–6.)
[r] Results are based on 295 patients: patients lost to follow-up and died during 12 months were excluded.
[s] In table 1 the percentage of patients with diabetes is 35.4%.

Table S2. General characteristics of dialysis-based studies

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
Ambrogi 2009	342	rates and patterns of eGFR evolution preceding dialysis initiation, divided in linear (N=185) and nonlinear decline (N=157)	AVENIR study, Loraine France (2005)	67.8 [±14.8]	61.1	44.4	N.R.	Original (186) 4-variable MDRD	10.0 [±9.7] months	20.3 [±16.9]	-13.2 [±2.1]	Linear: 9.1 [±3.2] Nonlinear: 10.8 [±3.6]
Beltrán 2009	63	identifying differences in survival between dialysis start after graft failure (GF, n=25) or native kidney failure (NF, n=38)	University hospital Dr Peset Valencia, Spain (1996)	GF: 63.5 [±13.6] NF: 56.8 [±19.5]	GF: 56 NF: 63.2	N.R.	HD	abridged MDRD	24 months	N.R.	GF: -0.83 [±0.4]/month NF: -0.42 [±0.2]/month	GF: 8.66 [±3.13] NF: 7.72[±2.32]
Bhan 2007	63	identifying factors associated with lack of access of fistula creation (with fistula creation n=30, without n=33)	Academic university hospital Dalhousie, Canada (2005)	With: 59 [±16] without: 64 [±15]	With: 80 without: 73	With: 43 without: 55	HD	MDRD, equation not specified	2	With: 13.3 [±6.1] Without: 18.0 [±8.4]	With: 0-1y:-4.7 [±3.5] 1-2y: 1.42 [±3.9] Without: 0-1y:-12.1 [±9.9] 1-2y: 0.54 [±10.4]	With: 7.5 [±3.5] Without: 8.6 [±3.3]

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
Eyre 2008	122	effects of low-protein diets (LPD, n=61) compared to controls (n=61) on nutritional status, morbidity, and mortality at the start of dialysis	Sahlgrenska University Hospital, Germany (1988)	Mean (range) LPD: 65.4 (37-85) Control: 64.3 (21-83)	67	N.R.	39% HD 61% PD	Original (186) 4-variable MDRD	6 months	N.R.	LPD: 4.08 [SEM ±0.48] Controls: 13.32 [SEM ±2.04]	LPD: 7.1 [±SEM 0.5] Controls: 6.9 [±SEM 0.4]
Haapio 2012	319	association between eGFR decline pattern and long-term survival on RRT	Finnish Registry for Kidney Diseases, Finland (1998)	Median 60 (IQR 47-69)	61	N.R.	37% PD	re-expressed (175) 4-variable MDRD	12 months	Median 13.3 (IQR 9.7;18.7)	-6.6 [±1.7] [c]	Median 7.1 (IQR 5.6;8.8)
He 2016	77	course of GFR decline 12 months before and after start of PD	Toronto General Hospital, Canada (2008)	63.1 [±15.1]	54.5	37.7	PD	original(186) 4-variable MDRD	1	N.R.	-0.59 [±0.55] per month	7.4 [±3.2]
Hsu 2016	661	quantify proportion of incident HD patients with an abrupt decline in kidney function prior to HD start and whether this pattern is associated with	CRIC study, USA (2003)	56.3 [±11.3]	61.3 (38.7 female)	70.5	HD	eGFR (CRIC equation)[d]	3.3 [±1.9]	32.6 [±10.4]	-6.7 [±2.5] [c]	10.4 [±4.4] [d]

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
		early death after initiating maintenance HD therapy										
Inaguma 2017	1292	association between eGFR decline in the 3 months prior to dialysis initiation and survival afterwards	AICOPP, Japan (2011)	67.8 [±12.9]	68.1 (31.9 female)	52.7	92.3% HD	eGFR[e]	3 months	8.72 [±4.63]	-12.96 [±15.76] [c, f]	5.48 [±2.11]
Jeong 2011	160	Case-control study comparing 80 patients with arteriovenous access (AVA) creation (=Z-point) before HD with 80 patients with catheter on rate of decline of renal function	University of Ulsan College of Medicine, Korea (2005)	AVA: 63.3 [±13.6] Catheter: 61.6 [±13.6]	55	55	HD	re-expressed (175) 4-variable MDRD	Before Z-point: 12 months after Z-point: AVA: 14.2 [±9.4] Catheter: 5.9 [± 4.1] months	On Z-point: AVA: 11.4 [±3.1] Catheter: 11.3 [±3.2]	Before Z-point AVA:-0.62 [±0.3] Catheter: -0.63 [±0.3] After Z-point AVF: -0.21 Catheter: -0.67 per month [g]	AVA: 6.4 [±2.0] Catheter: 6.1 [±1.9]
Jungers 2001	63	evaluation of the rate of kidney function decline and the duration of the predialysis period in	Necker Hospital, France (1990)	Epo+: 67.1 [±9.2] Epo-: 58.7 [±13.4]	Epo+: 50 (10/20) Epo-: 81 (35/43)	N.R.	Dialysis (modality unspecified)	Cockcroft-Gault	Months before T0: Epo+: 22.8 [±3.5] Epo-: 22.9 [±5.9]	Epo+: 10.2 [±1.7] Epo-: 11.9 [±2.4]	Before T0: Epo+: 0.36 [±0.16] Epo-: 0.55 [±0.48] T0-dialysis: Epo+: 0.26 [±0.15]	Epo+: 7.1 [±1.1] Epo-: 7.7 [±1.3]

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
		patients treated with recombinant erythropoietin (epo+, n=20) or not (epo-, n=43)							T0-dialysis: Epo+: 16.3 [±12.7] Epo-: 10.6 [±6.1]		Epo-: 0.57 [±0.44] Per month	
Kitai 2015	125	impact of nephrotic range proteinuria (with, n=103) versus without (n=22) on renal function decline during the 3 months prior to hemodialysis initiation	Osaka Red Cross Hospital, Japan (2008)	With-out: 71 [±9] With: 63 [±11]	With-out: 77.2 With: 72.8	100	HD	eGFR[e]	Median 75 (IQR 66-85) days	without: median 7.1 (IQR 5.9–8.6) with: median 6.2 (IQR 5.5–7.2)	Median 0.98 (IQR 0.51; 1.46) per month	Without: median 6.3 (IQR 5.1–8.0) With: median 5.2 (IQR 4.3–6.0)
Maeda 2011	112	examining effects of AST-120 (n=56) compared to controls (n=56) in suppressing CKD progression and delaying dialysis initiation	Juntendo University Hospital, Japan (2000)	Control: 62.9 [±13.0] AST: 61.0 [±12.9]	Control: 60.7 AST: 67.9	N.R.	Unclear	eGFR[e]	4	Control: 11.0 [±9.3] AST-120: 11.7 [±7.9]	Before baseline: Control: 0.722 [±0.885] AST-120: -1.041 [±1.177] After baseline: Control: -0.859 [±0.978] AST-120: -0.338 [±0.317] Per month	N.R.

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
O'Hare 2011	666	Estimating magnitude of changes in timing of dialysis initiation between 1997 and 2007[h]	Health care coorporation program; USRDS, US (1997 vs 2007)	64.2 [±14.1]	53.5	59.9	Unclear	Original (186) 4-variable MDRD	Median 1.9 (IQR 0.9;3.4)	N.R.	-6.7 (95%CI -7.1; -6.3)	8.2 [±4.7]
O'Hare 2012	5606	Investigating different eGFR trajectories in 2 years before long-term dialysis initiation	Veterans Affairs and US Renal Data System, US (2001)	66.2 [±11.5]	98.4 (1.6 women)	50.0	95.5 in-center HD	Original (186) 4-variable MDRD	Median 386 (IQR 179, 585) days	34.5 (pooled median, derived from figure 1)	13.5 [±13.1]	11.8 (pooled median derived from figure 1)
Ramspek 2017	197	Whether fast mGFR decline is a risk factor for mortality on dialysis, in contrast to a fast eGFR decline	NECOSAD-II, The Netherlands (1997)	58.3 [±14.3]	61.4	20.4	54.8% HD 45.2% PD	original (186) 4-variable MDRD	Median 204 (IQR 92-312) days	N.R.	Median 4.7 (IQR 1.8; 9.0)	7.3 [±2.6]
Sumida 2017	6540	comparing the rate of eGFR decline in patients with AVF/AVG (n=3026) and without	TC-CKD study, US (2007)	With-out: 67.0 [±10.8] With: 67.1 [±10.7]	With-out: 97.9 With: 98.0	With-out: 74.8 With: 74.9	HD	CKD-EPI	Median (IQR) Pre-AVF: Without: 1.7 (0.7, 2.9)	N.R.	Median (IQR) Pre-AVF: Without: −6.0 (−10.2, −3.3) With: −5.6 (−8.8, −3.4)	Median (IQR) Without: 13.0 (9.6, 17.7) With: 10.3 (8.0, 12.9)

First author and year of publication*	No. of parti-cipants	Aim of the study	Setting, country (year of baseline)	Mean [±SD] age[a]	% male	% DM	Dialysis modality	Renal function measure	Mean [±SD] duration of pre-dialysis period (years)[a]	Mean [±SD] initial / baseline eGFR (ml/min/1.73 m²)[a]	Unadjusted mean [±SD] of estimated annual decline (ml/min/1.73 m²/year)[a, b]	Mean [±SD] GFR at dialysis initiation/RRT (ml/min/1.73 m²)[a]
		(with catheter, n=3514)							With: 1.4 (0.5, 2.6) Post-AVF: Without: 0.5 (0.5, 0.5) With: 0.5 (0.2, 1.2)		Post-AVF: Without: −16.3 (−26.2, −9.5) With: −4.1 (−4.8, −3.2) [i]	
Sumida 2016	18 874	eGFR slopes prior to dialysis initiation with cause-specific mortality following dialysis initiation	TC-CKD study, US (2007)	69.1 [±11.3]	98.2	72.2	Unclear	CKD-EPI	Median 4.0 (IQR 3.0, 5.2)	N.R.	Median −5.4 (IQR −9.7, −2.9)	Median 13.0 (IQR9.5, 18.6)

Abbreviations:
N.R. not reported; HD=haemodialysis; PD=peritoneal dialysis, CKD=chronic kidney disease, RRT=renal replacement therapy, ESRD=end-stage renal disease
* Published between January 2000 and December 2016 (both finally published and epubs published in advance).
[a] Indicated as mean [±SD], unless indicated otherwise.
[b] Negative values represent a faster decline rate of GFR; positive values represent slower decline rate of GFR.
[c] Decline rate was calculated based on mean difference between initial baseline eGFR measure and GFR measured at the end of follow-up. In this case, meaning the difference between baseline eGFR and eGFR at dialysis initiation. Standard deviations of initial baseline eGFR value(s) were pooled with SDs from GFR value(s) at the end of follow-up. The derived mean ±SD was divided by the mean follow-up time (in years) to calculate the mean annual eGFR decline.
[d] reference for CRIC equation "Anderson AH, Yang W, Hsu CY, et al. Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2012;60(2):250-261"
[e] eGFR (ml/min/1.73 m2) = 194 x Serum creatinine$^{-1.094}$ xAge$^{-0.287}$ x 0.739 (if female). The mean (SD) eGFR at dialysis initiation was calculated over 493 patients.
[f] The eGFR value was calculated following the method described above in note [c]. In table 2 of the article, median (range) eGFR decline values for 3 months prior to dialysis initiation are described for G1 to G4. We reported the eGFR values at the beginning and at the end of follow-up (in this case the moment dialysis is started). This estimation is the most accurate, rather than pooling median (range) eGFR values over the 3 month period and multiply these by 4 to calculate the annual decline.
[g] In the article mean decline rates with SD are given before Z-point and after the Z-point the means are given without variance. Therefore, we calculated the mean [±SD] GFR decline by calculating the difference between eGFR values at the Z-point and at dialysis start, dividing these mean differences by the mean follow-up time from the Z-point to dialysis start (AVA: 14.2 [±9.4] months and controls: 5.9 [±4.1] months).
[h] Only the subgroup of patients was selected for whom a renal function decline was available.
[i] Adjusted eGFR decline: With: −18.1 (−20.6, −15.9) and −8.3 (−8.8, −7.5) Without: −20.6 (−23.5, −17.9) and −58.8 (−68.1, −51.6).

Table S3. Risk of bias assessment of included studies

CKD 3-5 cohorts

First author (year of publication)	Adequate definition and assessment of renal function decline	Adequate loss to follow-up (<10%)	Adequate selection of patients
Barrett 2015	-	-	?
Brown 2012	-	-	-
Chen 2011	-	?	-
Chen 2012	-	?	-
Chen 2013	-	?	-
Chen 2014	-	?	-
Chen 2015	-	?	?
Chen 2016	-	?	?
Chiu 2008	-	-	-
Chue 2011	-	+	?
Conway 2009	-	-	-
Datallo 2016	-	?	-
Drüeke 2006	+	+	?
Goicoechea 2010	-	-	?
De Goeij 2011	-	-	-
Golper 2015	-	-	-
Gouva 2004	+	-	?
Halimi 2016	-	+	?
Heaf 2011	-	?	-
Hsieh 2017	-	?	?
Inaguma 2016	-	-	?
Jones 2006	-	?	?
Kahn 2017	-	+	?
Kahn 2016	-	-	-
Kikuchi 2017	-	+	?
Kuo 2015	-	?	-
Levin 2008	-	?	-
Lewis 2004	-	?	?
Lim 2014	-	?	?
Lin 2013	-	+	?
Lucas 2008	-	?	?
McCaughan 2014	-	?	-
Meuleman 2015	-	+	?
Nacak 2015	-	?	-
Peeters 2014	-	-	?
Portoles 2013	-	+	?
Rigalleau 2007	-	?	?
Schulman 2015	-	?	?
Tan 2015	-	?	?
Tangkiatkumjai 2017	-	-	?
Tsai 2012	-	+	-
Tsai 2014	-	?	-
Xie 2016	-	?	-

?=unclear -=low risk of bias +=high risk of bias

Dialysis-based studies

First author (year of publication)	Adequate definition and assessment of renal function decline	Adequate selection of patients
Ambrogi 2009	-	-
Beltrán 2009	-	?
Bhan 2007	-	-
Eyre 2008	-	?
Haapio 2012	-	-
He 2016	-	-
Hsu 2016	-	?
Inaguma 2017	-	?
Jeong 2011	-	?
Jungers 2001	+	?
Kitai 2015	-	-
Maeda 2011	-	?
O'Hare 2011	-	-
O'Hare 2012	-	-
Ramspek 2017	-	-
Sumida 2017	-	-
Sumida 2016	-	-

?=unclear -=low risk of bias +=high risk of bias

CHAPTER 3

INCIDENT VERSUS PREVALENT DIALYSIS COHORTS: THE RISK OF SELECTION BIAS

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ABSTRACT

Many studies assess the effect of risk factors on health outcomes, for instance the effect of cardiovascular disease on mortality in dialysis patients. Some of these studies include new patients starting dialysis, also referred to as *incident patients*, while other studies cross-sectionally include patients already on dialysis at a certain moment in time, also referred to as *prevalent patients*. These two methods of selecting patients may have consequences for the interpretation and the validity of the study results. In a cohort with prevalent dialysis patients, these patients have spent a varying amount of time on dialysis already and only those who survived until cohort entry are included. This selection could introduce bias if the risk factor under study (for example cardiovascular disease) is also related to selection. This paper first explores to what extent estimations of risk factor-outcome associations differ when selecting a prevalent compared to an incident dialysis cohort. Second, selection bias is considered as a potential explanation for these differences.

INCIDENT AND PREVALENT COHORTS

In many studies, the effect of a risk factor on a health-related outcome is assessed. An example is the effect of anemia on mortality in dialysis patients. Such an etiologic study is usually performed within a cohort of dialysis patients, by comparing patients with to patients without the risk factor (anemia versus non anemia), or between levels of the risk factor. From a practical point of view there are two ways to sample such cohorts for risk factor studies (incident and prevalent dialysis patients, see below), and in this paper we discuss the consequences of such cohort sampling for the validity of a risk factor study.

Suppose the association of cardiovascular disease with all-cause mortality in a cohort of dialysis patients is studied. In general, a cohort of dialysis patients could be sampled in two ways. Firstly, patients could be included and followed from dialysis initiation onwards, as illustrated by the dots in figure 1. In this situation, patients A to F are included. Each patient will be included in the cohort at the same moment in the disease course (here: at start of dialysis), but at a different moment in calendar time. These patients are so called *incident patients*, in this situation 'incident dialysis patients', and the cohort is referred to as an incident cohort. For didactic purposes, we assume that the exposure variable of interest (for example cardiovascular disease or anemia), is measured at baseline, i.e. at start of dialysis.

In a second approach, all patients on dialysis at a single point in calendar time are included, as illustrated by the dashed line in figure 1. In this situation patients B to E are included, and as a consequence of this sampling approach patients show a varying dialysis vintage at cohort entry. These included patients are *prevalent patients*, and the accompanying cohort is referred to as a prevalent cohort. The term prevalent refers to their status as 'prevalent dialysis patients'. For some patients (patient C) the moment of inclusion is very close to the start of dialysis, for others (patient E) more time elapsed. In these prevalent patients, the risk factor of interest (here cardiovascular disease) is also assessed at baseline, which in this case is the moment of inclusion in this cohort of prevalent patients. Mind that also a combination of approaches can be applied, if inclusion starts at a specific point in calendar time (thereby including prevalent dialysis patients), and subsequently new, incident, patients are included for a period of calendar time. In any case, the method of selecting patients in a cohort may have consequences for the interpretation and validity of study results.

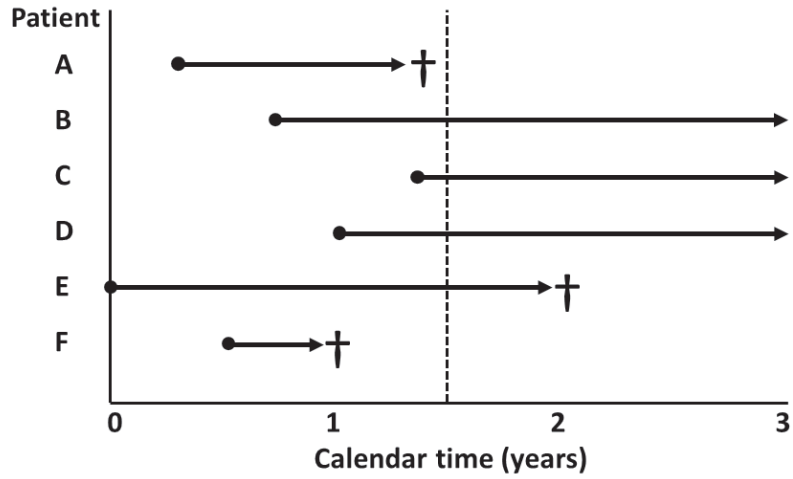

Figure 1. Selection of an incident versus a prevalent dialysis patient population. Notes: In an incident cohort, dialysis patients are followed from the start of dialysis, represented by the black dot. The cohort entry for these incident patients is at a varying point in time. A prevalent cohort could be assembled at one moment in time, i.e. a specific date, represented by the dashed line. All patients are selected at the same moment in time, but with varying dialysis vintage. As may be clear, patients A and F are not included in the prevalent cohort.

To illustrate, the Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD) is an example of an incident cohort, in which all patients who started dialysis between 1997 and 2007 were included at start of dialysis initiation.[1] The Dialysis Outcomes and Practice Patterns Study (DOPPS I) is an example of a prevalent cohort[2], as in this study various countries included a cross-sectional sample of hemodialysis patients; these patients thus already received dialysis for some time at cohort entry. DOPPS I later became DOPPS II, in which besides prevalent patients also new, incident, patients were included.[2] This combined approach will not further be considered here.

Key methodological articles have elaborated on the difference between incident and prevalent patients, for example when studying drug effects.[3, 4] Moreover, some empirical studies in other fields showed that considerable differences may exist between the two cohorts and argued for the use of incident cohorts derived from whole populations.[5-7] However, there is a lack of studies in nephrology that empirically demonstrate the consequences of selecting an incident versus a prevalent cohort for effect estimations of risk factors. Therefore, this paper first explores to what extent estimations of risk factor-outcome associations differ when selecting a prevalent compared to an incident cohort of dialysis patients for assessing effects of a series of classical risk factors for mortality. Second, selection bias is considered as a potential explanation for these differences.

EXAMINING THE DIFFERENCES IN RISK FACTOR-OUTCOME ASSOCIATIONS BETWEEN INCIDENT AND PREVALENT COHORT

Methods

For this purpose, we compared the effect estimates for the association of a series of predefined risk factors with all-cause mortality between incident and prevalent dialysis patients. We used data from one population, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort[1,8], to compile both an incident and a prevalent cohort. In the NECOSAD study new patients were included at the start of dialysis between 1997 and 2007, and follow-up data on death were available until April 2019. From this originally incident cohort, we sampled prevalent patients for the sole aim of the present analysis. The prevalent cohort consisted of all patients alive and on dialysis at the reference date of January 1st, 2004.

To study the differences in estimations, we examined the association between *a priori* selected potential risk factors and all-cause mortality in dialysis patients using Cox regression. Hazard ratios (HRs) and 95% confidence intervals (95%CI) were reported. We studied the following risk factors: sex, cardiovascular disease, obesity, diabetes, anemia, serum phosphate, serum calcium, and nutritional status. Hazard ratios were adjusted for potential confounders, depending on the risk factor under study (for details see the method section in the Supplements). For the incident cohort the values of these factors at start of dialysis were used, while for the prevalent sampled cohort the value of these factors was used close to the reference date. The potential impact of the sampling method was investigated by comparing HRs between the incident and prevalent sampled cohort.

When the exposure under study is indeed a risk factor for mortality, patients with that exposure are less likely to be included in a prevalent cohort compared to patients without the exposure, as they are more likely to have already died. Consequently, the potential impact of selecting prevalent versus incident patients could also be revealed by comparing the difference in risk factor prevalence between these two study populations, in which situation the risk factor prevalence is expected to be lower in the prevalently sampled cohort.

To confirm the robustness of our findings, we repeated the analysis for incident patients included only within a limited time window between the 1st of January 2001 and 2007. In a further sensitivity analysis, the reference date for the prevalent cohort was set on January 1st, 2002 instead of 2004. For a detailed description of these methods, we refer to the Supplements.

Results

2044 incident patients were included, from which 475 prevalent patients were sampled. In figure 2 hazard ratios of risk factor-mortality associations for different risk factors are presented for both incident and prevalent patients. In all instances the confidence intervals for the prevalent cohort were wider, which is a reflection of the smaller sample size of the prevalent sample.

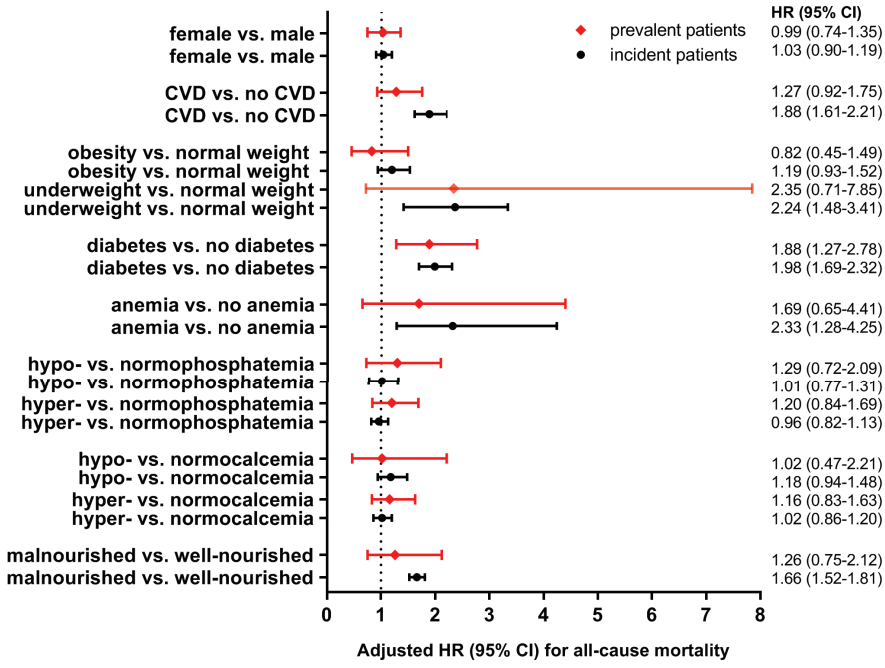

Figure 2. Impact of selecting prevalent versus incident dialysis patients when investigating the association between baseline risk factors and mortality.
Notes: Incident patients represent a larger sample, because prevalent patients are selected from an incident cohort. Associations between each risk factor and all-cause mortality were adjusted for a set of potential confounders, depending on the risk factor under study (see legend of Table S1 for more details). Hazard ratios for prevalent patients were also adjusted for the dialysis vintage.
Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

Figure 2 shows substantial differences in effect estimates between the incident and prevalent cohort. However, the differences vary in size and direction, ranging from weaker effects, to no difference, to stronger effects, to even opposite effects. On the whole, for most risk factors the effect estimates in the prevalent cohort are closer to 1 than in the incident cohort. For the risk factor CVD, for example, we see in figure 2 that the HR (95%CI) for mortality, when comparing patients with to patients without CVD, was 1.88 (1.61-2.21) for the incident cohort and 1.27 (0.92-1.75) for the prevalent cohort. Also, for the risk factor malnourishment (versus

well nourished), a higher HR for mortality was seen for incident patients versus prevalent patients (HR 1.66 versus 1.26). For the risk factor sex, however, HRs for mortality do not differ between the incident and prevalent cohort (HR 1.03 versus 0.99), while for the risk factor obesity (versus normal weight) even a small survival benefit was seen for prevalent patients and a survival disadvantage for incident patients (HR 0.82 versus 1.19).

For the same set of risk factors, we compared the difference in risk factor prevalence in the prevalent and incident study population. Results are shown in figure 3. For instance, a considerably lower percentage of prevalent patients was exposed to the risk factor malnourishment (28% versus 15%). No large difference in sex-distribution between the incident and prevalent population was seen (41% versus 38% female).

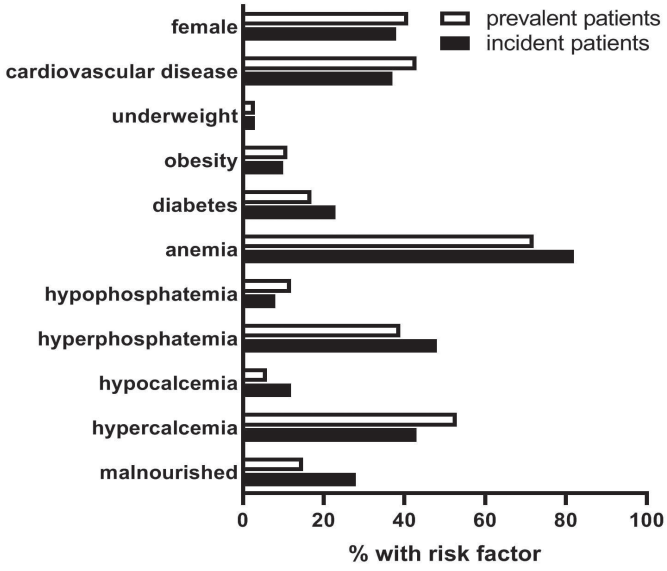

Figure 3. Prevalence of risk factors in the incident and prevalent population.

To confirm the robustness of our observations, we repeated the main analysis in a subgroup of incident patients included from January 1st of 2001 until 2007. Applying this restriction yielded comparable results (figure S1 and S2). Furthermore, adjusting the cohort entry date of the prevalent cohort yielded comparable results, except for the effect of cardiovascular disease on all-cause mortality. Here, similar hazard ratios were observed for prevalent and incident dialysis patients (figure S3 and S4).

DIFFERENCES EXPLAINED: THE RISK OF SELECTION BIAS IN PREVALENT COHORTS

This paper highlights the potential differences in effect estimates for a range of clinical risk factors in association to all-cause mortality when comparing a prevalent to an incident dialysis population. We found that effect estimates may differ substantially, most often resulting in weaker effects in prevalent than incident patients, but varying to stronger effects and even opposite effects. In line, we showed differences in the risk factor prevalence in prevalent and incident patients that could be considerable.

The fact that effect estimates differ may seem rather logical. For example, consider the effect of the risk factor diabetes on mortality. We might infer that most diabetic patients will have died before inclusion into the prevalent cohort, and therefore the effect of diabetes on mortality will be weaker in prevalent than in incident patients. However, this is a clear and quite common misconception. After all, just the fact that the group of diabetic patients is smaller in the prevalent cohort is insufficient to explain that the effect of their diabetes on mortality would be smaller as well.

Still, a little intuition goes a long way when trying to understand how the observed differences came about. The fact that a diabetic patient still makes it into a prevalent cohort, and thus has survived until he was selected into that cohort, despite his diabetes, seems to imply there must be something special about this patient. Perhaps he has something extra, something protective, or maybe he lacks other risk factors, making him seemingly resistant to his diabetes. This would obviously result in a different effect estimate for diabetes on mortality in the prevalent cohort than in the incident cohort.

More formally, such differences may arise as a consequence of selection bias. In a prevalent dialysis cohort, patients must have survived a certain amount of time in order to be included in the cohort. As can be seen from figure 1, patients A and F died before date of sampling and were by design not included in the prevalent cohort. Patients dying early in the dialysis course will have more mortality-related risk factors than patients who survived until sampling in the prevalent cohort. Now consider the study of a risk factor (factor X) and its effect on mortality. Patients with this risk factor X included in a prevalent cohort, and thus having survived until sampling, are less likely to have other risk factors for mortality, given that they have survived. After all, if they had multiple risk factors for mortality, they most likely would not have survived until sampling. Thus, if in a prevalent cohort, patients with the risk factor X are compared to

patients without X, we are basically making an unfair comparison and the risk estimation is likely biased.[11] The prevalent patients with risk factor X are on average healthier than those without, or they would not have made it into the prevalent cohort. Thus, the patients included in the prevalent cohort are not a random sample of all patients in the incident cohort. This form of selection is also called depletion of the susceptibles.[12, 13]

As prevalent patients with risk factor X are less likely to have other risk factors for mortality there is a problem of incomparability. Part of this incomparability will be solved by adjusting for confounding factors: the risk factors for mortality that are also risk factors for the exposure X under study. However, there are usually other factors (U) that are risk factors for the outcome that are not confounding factors, but that are related to being selected as a prevalent patient. These factors U differ from confounding factors in a sense that they are not related to the exposure X under study, only to the outcome. Thus even though X and U are unrelated in the whole patient population, when studying the effect of X within the prevalent selection, we are creating an artificial association between X and U: the fact that someone with risk factor X survived until sampling into the prevalent cohort, makes him less likely to also have risk factor U. Thus, importantly, the fact that the selection of patients is associated with the risk factor X in itself does not necessarily bias the estimates of the risk factor-outcome association. Selection bias will arise when there are other factors U that determine patient selection and are also a risk factor for the outcome. Still, when all such factors U are measured, adjustment for these covariates is possible and would remedy selection bias.[9] (Note that in general we would not necessarily think to adjust for these factors as they are not confounders.) However, part of these factors U may be unmeasured. Because we cannot adjust for these unmeasured covariates, obtained risk factor-outcome associations could be biased. A graphical display of this form of selection bias is presented in a directed acyclic graph (DAG) in figure S5 in the supplements.

As an example, think of a study assessing the mortality risk of cardiovascular disease (X) in prevalent dialysis patients. Generally, cancer (U) would not be considered a confounder as it is not a risk factor for cardiovascular disease. However, cancer and cardiovascular disease are both related to selection (being a prevalent dialysis patient); both patients with cancer and patients with cardiovascular disease will likely die before being selected as a prevalent patient. Now, when assessing the effect of cardiovascular disease on mortality within prevalent patients, we are looking at a group of patients that has survived until selection despite their cardiovascular disease. This means they probably do not also have cancer. Hence, by selecting prevalent patients we have created an artificial (inverse) association between cardiovascular

disease and cancer, and in this case the analysis should adjust for difference in cancer prevalence to remedy selection bias, even though cancer itself is not a confounder. Next, consider the example of malnutrition and mortality. Again, if the factors U that determine survival are known and well measured, then the malnutrition-mortality association estimated in a prevalent cohort is unbiased if properly adjusted for the variables U. However, if these variables U are unmeasured, then adjustment is not possible. For instance, if a genetic predisposition favors the selection of a subgroup of patients, but genetic information is frequently missing, then the malnutrition-mortality association will be biased.[10] In general, when the outcome under study is mortality, risk factors for the outcome will always be related to being selected as a prevalent patient, and it is thus best to correct for as many measured risk factors for the outcome as possible, as long as they are not in the causal pathway.

Now, the observed differences for the different risk factors can be viewed in light of the relation of the risk factor with the selection, and the potential existence of unmeasured factors U. For example, we would expect that the risk factor sex is not related to being selected as a prevalent dialysis patient, and therefore we expected a negligible difference in observed HRs between the prevalent and incident cohort. Indeed, the adjusted HRs for the risk factor sex were similar between the incident and prevalent cohort, and also the sex-distribution between the incident and prevalent population was similar (41% versus 38% female). In contrast, we expected that the risk factors nutritional status and CVD were related to being selected into the prevalent dialysis cohort and this association with the selection, combined with the likely existence of unmeasured factors U, would influence the observed HRs in the incident versus prevalent cohort. A higher adjusted HR was expected in incident patients than in prevalent patients, because the more healthy patients are included in the prevalent cohort and will be at lower risk for mortality. For the risk factor CVD, we did see in figure 2 that the adjusted HR (95%CI) for mortality, when comparing patients with to patients without CVD adjusted for usual confounders, was 1.88 (1.61-2.21) for the incident cohort and only 1.27 (0.92-1.75) for the prevalent cohort. Similarly, the risk for mortality due to malnourishment was higher in incident sample compared to the prevalent sample (1.66 versus 1.26) and the prevalence of malnourishment was also higher (28% versus 15%).

A well-known example from literature to highlight selection bias in a prevalent cohort is a phenomenon called the 'obesity paradox'. More specifically, obesity is a well-known risk factor for mortality, although it has occasionally been shown to be associated with a survival benefit as compared with normal weight. This phenomenon is also seen in our results where a survival benefit is seen in the prevalent patients and obesity is a risk factor for mortality in our incident dialysis patients. One of the possible explanations is selection bias: if patients with obesity have survived until inclusion in a prevalent cohort, they will on average have a lower prevalence of other mortality risk factors. If these factors are unmeasured or not adjusted for properly, selection bias may occur in a study where mortality is the outcome.

Several limitations of this empirical exploration should be acknowledged. Due to the incident cohort design of NECOSAD fewer patients were sampled in the prevalent cohort and obtained confidence intervals were wider, reflecting this smaller sample size. Moreover, for the prevalent cohort risk factor measurements were used up till 3 months prior the start of the cohort (January 1st 2004), while in a prospective prevalent cohort baseline variables would be assembled on the inclusion date. Furthermore, our results are possibly influenced by calendar effects, including different patient characteristics and dialysis modalities over time. Yet, the sensitivity analyses, in which we applied another time window for the patient inclusion of the incident cohort and another cohort entry reference date of the prevalent cohort, yielded comparable results. Finally, we did not explore the impact of variables U that are risk factors for the outcome and related to selection, which are necessary for the occurrence of selection bias, on the difference in effect estimates.

To conclude, we showed that crude risk factor estimates could differ considerably between prevalent and incident patients - even after adjustment for measured covariates associated with the outcome and selection - which may be explained by selection bias. Selection bias should be considered when the risk factor under study is associated with the selection of patients. In practice, investigators generally perform one study, either prevalent or incident study and do not compare study results, in which situation it is unknown whether and how much the effect estimates are influenced by selecting prevalent patients. Selection bias can in principle be remedied by statistical adjustment for covariates associated to both the outcome and the selection (whether or not they are related to the risk factor under study), provided they have all been measured appropriately. However, as this is unlikely in general, we would argue for the use of incident cohorts when studying these risk factor-outcome associations.

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SUPPLEMENTS

1. SUPPLEMENTAL INFORMATION

METHODS

Study design and population

Netherlands Cooperative on the Adequacy of Dialysis-2 (NECOSAD) was a multicenter prospective observational cohort study in which 38 Dutch dialysis centers participated. Patients were included between 1997 and 2007, and follow-up data on death were available until April 2019. Patients were followed until time of death or censored, due to kidney transplantation, recovery of kidney function as reason to stop dialysis therapy, withdrawal from the study, transfer to a dialysis center that did not participate in the study, loss to follow-up, or end of the study period, whichever came first. The Medical Ethics Committee of the Academic Medical Center in Amsterdam (as coordinating center of the NECOSAD study) approved the study for all participating hospitals, and all hospitals involved approved participation. The study was conducted according to the Declaration of Helsinki. All patients gave written informed consent.

Incident and prevalent patient population

With incident patients, we mean a study with the cohort's inception date according to patients' initiation date of dialysis. With prevalent patients, we mean patients already receiving dialysis at the moment of cohort entry, independent of the dialysis vintage.[1] To emulate a cohort with prevalent dialysis patients, the date of cohort entry was set at January 1st 2004. Since prevalent patients are extracted from an incident patient cohort on this reference date, the prevalent cohort is smaller than the incident cohort.

Risk factors and outcome

We studied the risk factors sex, cardiovascular disease, obesity, diabetes, anemia, serum phosphate levels, serum calcium levels and nutritional status on the outcome all-cause mortality. For all risk factors we determined the 5-year all-cause mortality. For anemia we determined the 1-year mortality, because a short term effect on mortality was expected. For the current analyses, patients were included if the prespecified determinant and outcome were measured. For the prevalent dialysis patients, risk factors and baseline confounders were selected in the 3 month time window around the cohort entry date of January 1st 2004.

Variable definitions

The definitions of the risk factors under study are described below. The presence of *cardiovascular comorbidity* was defined as having one or more of the following clinical diagnoses: angina pectoris, previous myocardial infarction, congestive heart failure, previous cerebrovascular incident or overt peripheral vascular disease. *Obesity* was defined as having a BMI ≥ 30 kg/m^2, underweight was defined as having a BMI < 18.5 kg/m^2, normal weight was defined as having a BMI of 18.5-30 kg/m^2.[2] *Diabetes* was defined as having the comorbidity diabetes or having been diagnosed with diabetes as primary kidney disease. *Anemia* is defined as hemoglobin level < 12 g/dl for women and < 13g/dl for men. *Serum phosphate* levels were divided in three categories: hypophosphatemia (<1.13 mmol/l), normophosphatemia (1.13-1.78 mmol/l), hyperphosphatemia (>1.78 mmol/l).[3] *Serum calcium* levels were divided in three categories: hypocalcemia (<2.10 mmol/l), normocalcemia (2.10-2.37 mmol/l), hypercalcemia (>2.37 mmol/l).[3] To convert phosphate levels in mmol/l to mg/dl, multiply by 3.1 and to convert calcium levels in mmol/l to mg/dl, multiply by 4. *Nutritional status* was measured with the 7-point subjective global assessment (SGA), for more details see previous publication of de Mutsert *et al*.[4] Nutritional status was defined as malnourished with SGA score of 1 to 5 and as well-nourished with SGA scores 6 or 7.

The definitions applied for the confounders are described below. Treatment modality was defined as either receiving haemodialysis or peritoneal dialysis. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[5] Information on comorbidities included in the Khan score was collected by using questionnaires completed by clinicians and was based on clinical diagnosis and information on comorbidities from patient records. The Khan comorbidity score includes the following risk groups: low risk is defined as age < 70 years and no comorbid illness; medium risk is defined as age 70-80 years or age < 80 years with any one of the following: cardiac, pulmonary or liver disease or age < 70 years with diabetes mellitus; high risk is defined as age > 80 years or any age with two or more organ dysfunctions in addition to end-stage renal disease or any age with visceral malignancy.[6]

Statistical analyses

Multiple imputation was used to deal with missing data of confounders.[7-9] HRs and standard errors were estimated in each imputation set and pooled into one overall estimate and standard error according to Rubin's rules.[10, 11] Multiple imputation was applied, using a fully conditional specification with 10 repetitions. In the multiple imputation model, we included all

potential confounders, risk factors, outcome and time to outcome. Non-normally distributed variables were transformed to approximate normality before imputation and then the imputed values were transformed back to the original scale.[8]

We performed Cox proportional hazards regression analyses for examining the effect of several baseline risk factors on mortality in both the prevalent and incident patient population. Unadjusted and adjusted hazard ratios for risk of death were obtained. With adjusted hazard ratios, adjustment for potential confounders is meant, not adjustment for other factors U. Different confounders were considered to assess the associations between each risk factor and the outcome mortality. This concerns the following list of confounders, represented as *risk factor:* confounders. *Sex:* age at baseline; *Cardiovascular disease:* age, sex, ethnicity, smoking status, treatment modality, primary kidney disease at baseline; *Obesity:* age, sex, ethnicity, smoking status, treatment modality, primary kidney disease at baseline; *Diabetes:* age, sex, ethnicity, smoking status, treatment modality at baseline; *Anemia:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin at baseline; *Serum phosphate:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin, serum calcium, serum iPTH, nutritional status and serum hemoglobin at baseline; *Serum calcium:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin, serum phosphate, serum iPTH, nutritional status and serum hemoglobin at baseline; *Nutritional status:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease at baseline.

To confirm the robustness of our findings, we repeated the analysis for incident patients included only between January 1st of 2001 until 2007. Furthermore, the reference date for cohort entry of prevalent patients was set on January 1st, 2002 instead of 2004.

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Table S1. Impact of selecting prevalent versus incident patients when investigating the association between different baseline risk factors and all-cause mortality in dialysis patients.

	Prevalent patients				Incident patients		
	N	Unadjusted HR (95% CI)	Adjusted HR (95% CI) Model 1 [a]	Adjusted HR (95% CI) Model 2 [b]	N	Unadjusted HR (95% CI)	Adjusted HR (95% CI) Model 1 [a]
Sex	**474**				**2044**		
Male	282	1	1	1	1270	1	1
Female	192	0.98 (0.73-1.33)	0.98 (1.03-1.07)	0.99 (0.74-1.35)	774	1.02 (0.89-1.18)	1.03 (0.90-1.19)
Cardiovascular disease	**475**				**1825**		
No	273	1	1	1	1146	1	1
Yes	202	1.76 (1.31-2.37)	1.31 (0.95-1.81)	1.27 (0.92-1.75)	679	2.88 (2.48-3.33)	1.88 (1.61-2.21)
Weight	**350**				**1748**		
Underweight	9	1.70 (0.54-5.37)	2.81 (0.85-9.29)	2.35 (0.71-7.85)	53	1.30 (0.86-1.96)	2.24 (1.48-3.41)
Normal weight	301	1	1	1	1524	1	1
Obesity	40	0.86 (0.49-1.50)	0.89 (0.50-1.61)	0.82 (0.45-1.49)	171	1.27 (1.00-1.60)	1.19 (0.93-1.52)
Diabetes	**475**				**1824**		
No	395	1	1	1	1411	1	1
Yes	80	1.21 (0.85-1.73)	1.63 (1.12-3.36)	1.88 (1.27-2.78)	413	2.01 (1.73-2.35)	1.98 (1.69-2.32)
Anemia	**436**				**1912**		
No	123	1	1	1	351	1	1
Yes	313	2.47 (1.04-5.84)	1.67 (0.64-4.34)	1.69 (0.65-4.41)	1561	3.36 (1.87-6.03)	2.33 (1.28-4.25)
Serum phosphate	**436**				**1918**		
Hypophosphatemia	53	1.16 (0.70-1.91)	1.27 (0.75-2.15)	1.29 (0.72-2.09)	159	1.23 (0.96-1.57)	1.01 (0.77-1.31)
Normophosphatemia	215	1	1	1	848	1	1
Hyperphosphatemia	168	1.09 (0.79-1.51)	1.15 (0.81-1.63)	1.20 (0.84-1.69)	911	0.89 (0.77-1.04)	0.96 (0.82-1.13)

	Prevalent patients				Incident patients		
	N	Unadjusted HR (95% CI)	Adjusted HR (95% CI) Model 1 [a]	Adjusted HR (95% CI) Model 2 [b]	N	Unadjusted HR (95% CI)	Adjusted HR (95% CI) Model 1 [a]
Serum calcium	**438**				**1919**		
Hypocalcemia	26	1.12 (0.54-2.32)	1.17 (0.54-2.50)	1.02 (0.47-2.21)	229	1.40 (1.14-1.73)	1.18 (0.94-1.48)
Normocalcemia	178	1	1	1	874	1	1
Hypercalcemia	234	1.17 (0.85-1.59)	1.28 (0.92-1.78)	1.16 (0.83-1.63)	816	0.79 (0.68-0.93)	1.02 (0.86-1.20)
Nutritional status	**302**				**1611**		
Well-nourished	256	1	1	1	1162	1	1
Malnourished	46	1.39 (0.86-2.23)	1.37 (0.80-2.34)	1.26 (0.75-2.12)	449	1.98 (1.68-2.33)	1.66 (1.52-1.81)

Abbreviations: N = number of patients included in analysis; HR, hazard ratio; CI, confidence interval.
Notes: [a] In model 1 we adjusted for different confounders for each risk factor under study, represented as *risk factor:* confounders adjusted for. *Sex:* age at baseline; *Cardiovascular disease:* age, sex, ethnicity, smoking status, treatment modality, primary kidney disease at baseline; *Obesity:* age, sex, ethnicity, smoking status, treatment modality, primary kidney disease at baseline; *Diabetes:* age, sex, ethnicity, smoking status, treatment modality at baseline; *Anemia:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin at baseline; *Serum phosphate:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin, serum calcium, serum iPTH, nutritional status and serum hemoglobin at baseline; *Serum calcium*: age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease, serum albumin, serum phosphate, serum iPTH, nutritional status and serum hemoglobin at baseline; *Nutritional status:* age, sex, ethnicity, smoking status, treatment modality, khan comorbidity score, primary kidney disease at baseline. [b] Model 2 was adjusted for all variables as mentioned for model 1 plus dialysis vintage.

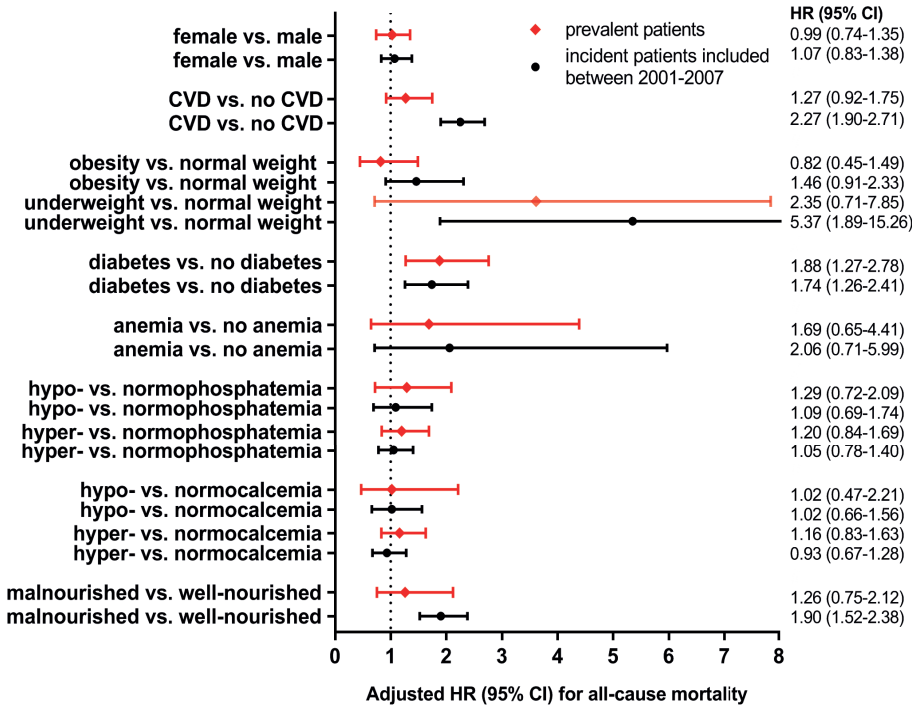


Figure S1. Impact of selecting prevalent versus incident dialysis patients when investigating the association between baseline risk factors and all-cause mortality (sensitivity analysis-1).

Notes: Incident patients starting dialysis only between January 1, 2001-2007 were included for this sensitivity analysis. This resulted in a lower number of incident patients compared to Figure 2. Associations between each risk factor and mortality were adjusted for a set of potential confounders, depending on the risk factor under study (see legend of Table S1 for more details). The HR's for prevalent patients were also adjusted for dialysis vintage.

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

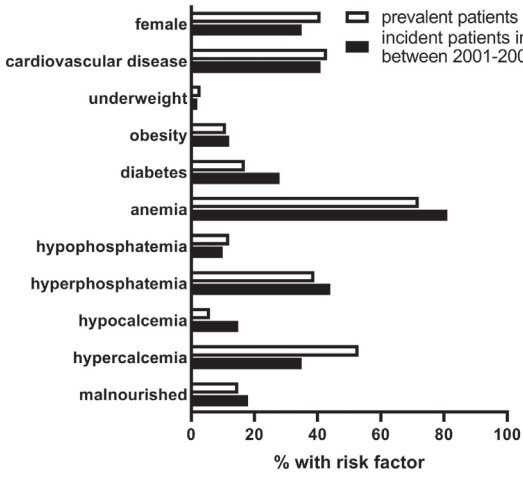


Figure S2. Prevalence of risk factors in the incident and prevalent population.
Notes: Incident patients included only between January 1, 2001-2007 were included for this sensitivity analysis. This resulted in a lower number of incident patients compared to Figure 2

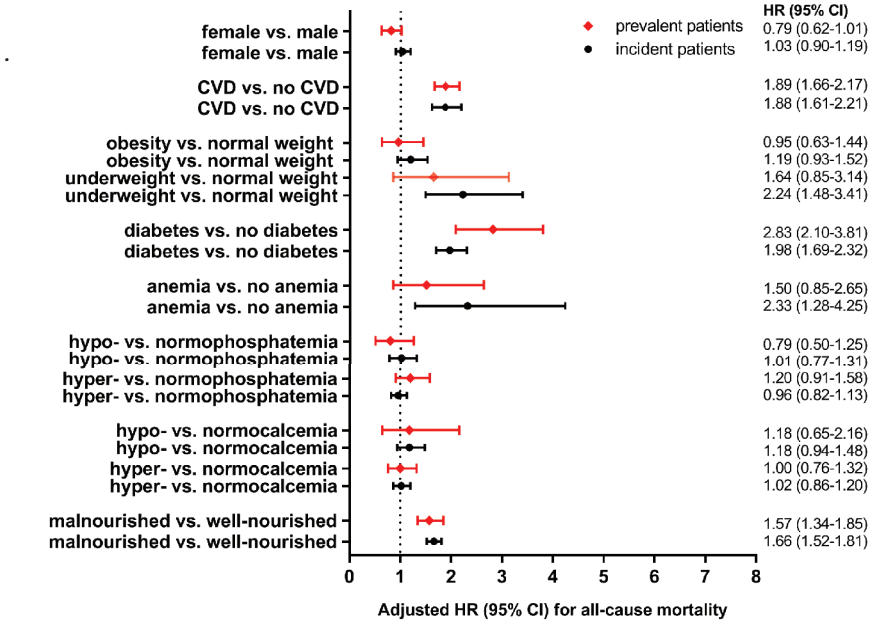


Figure S3. Impact of selecting prevalent versus incident dialysis patients when investigating the association between baseline risk factors and all-cause mortality (sensitivity analysis-2).
Notes: Incident patients represent a larger sample, because prevalent patients are selected from an incident cohort. The cohort entry of prevalent patients for this sensitivity analysis was defined as January 1st, 2002 instead of 2004. Associations between each risk factor and mortality were adjusted for a set of potential confounders, depending on the risk factor under study (see legend of Table S1 for more details). The HR's for prevalent patients were also adjusted for dialysis vintage.
Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

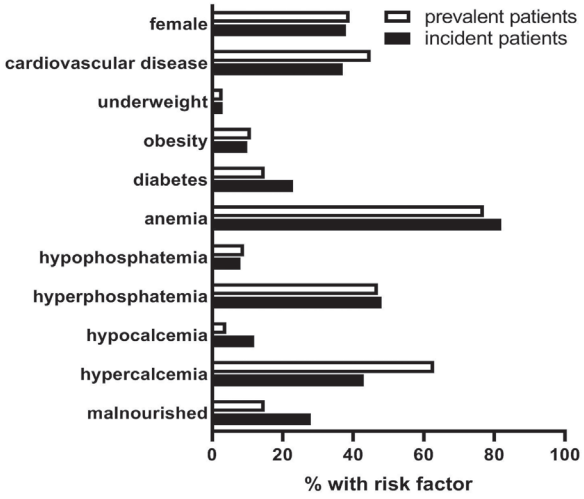


Figure S4. Prevalence of risk factors in the incident and prevalent population.
Notes: The cohort entry of prevalent patients for this sensitivity analysis was defined as January 1st, 2002 instead of 2004.

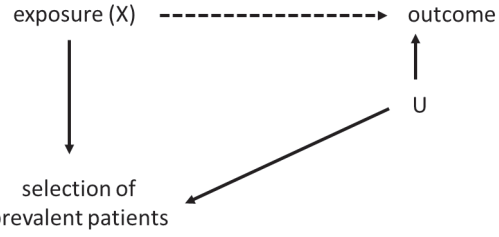
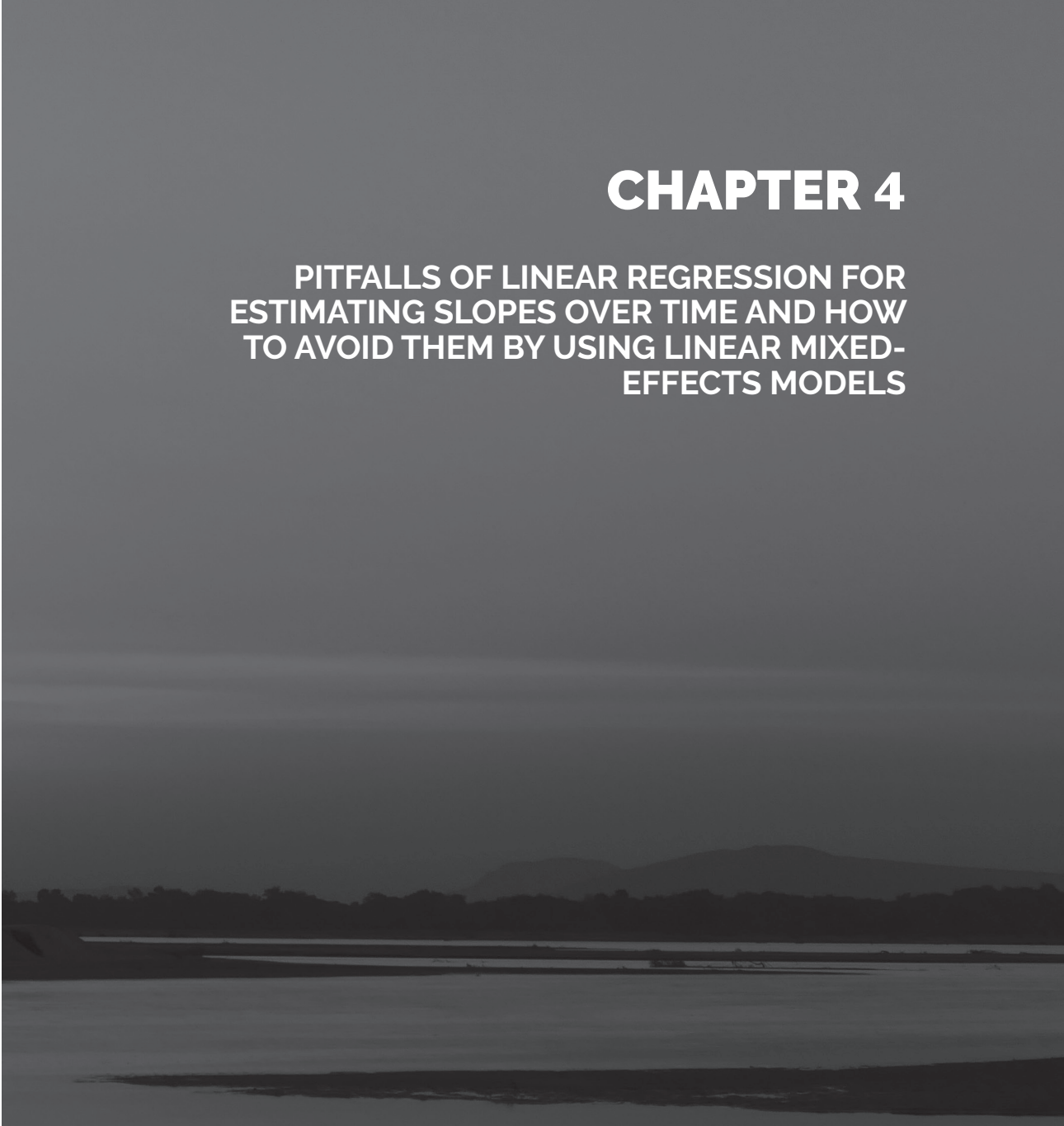


Figure S5. Selection bias in a prevalent dialysis cohort.
Notes: Selection bias is illustrated in a directed acyclic graph (DAG). By selecting or restricting to the prevalent dialysis patients, an association could be introduced between exposure (X) and outcome, while not representing the true association. This biased association is introduced by an open path between exposure X and the outcome via unmeasured covariates U. Technically, this is called an open backdoor path between exposure X and the outcome by conditioning on a collider (selected patients).
Abbreviations: U = unmeasured covariates.

CHAPTER 4

PITFALLS OF LINEAR REGRESSION FOR ESTIMATING SLOPES OVER TIME AND HOW TO AVOID THEM BY USING LINEAR MIXED-EFFECTS MODELS



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ABSTRACT

Clinical epidemiological studies often focus on investigating the underlying causes of disease. For instance, a nephrologist may be interested in the association between blood pressure and the development of chronic kidney disease (CKD). However, instead of focusing on the mere occurrence of CKD, the kidney function decline over time might be the outcome of interest. For examining this kidney function trajectory, patients are typically followed over time with their kidney function estimated at several time points. During follow-up, some patients may drop out earlier than others and for different reasons. Furthermore, some patients may have a higher kidney function at study entry or a faster kidney function decline than others. Also, a substantial heterogeneity may exist in the number of kidney function estimates available for each patient. This heterogeneity with respect to kidney function, dropout and number of kidney function estimates is important to take into account when estimating kidney function trajectories. In general, two methods are used in literature to estimate kidney function trajectories over time: linear regression to estimate individual slopes and linear mixed-effects model (LMM), i.e. repeated measures analysis. Importantly, the linear regression method does not properly take into account above-mentioned heterogeneity, whereas the LMM is able to retain all information and variability in the data. However, the underlying concepts, use and interpretation of LMMs is not always straightforward. Therefore, we illustrate this using a clinical example and offer a framework how to model and interpret the LMM.

INTRODUCTION

In epidemiological research, studies often focus on investigating risk factors for diseases. For instance, the effect of blood pressure or glycated hemoglobin A_{1c} (HbA_{1c}) levels on the development of end-stage renal disease is investigated.[1, 2] In addition to the mere occurrence of end-stage renal disease, clinicians may also be interested in chronic kidney disease (CKD) progression. Then, one might study the effect of blood pressure or HbA_{1c} levels on CKD progression, in other words the kidney function decline or, more generally, the trajectory of kidney function over time.[3-10] When investigating trajectories of kidney function, patients are typically followed over time with their kidney function estimated at several time points. In addition, the number of estimated glomerular filtration rate (eGFR) values may vary across patients. Also, during the follow-up, some patients may drop out during the study and thus their follow-up period is terminated earlier than intended. Furthermore, some patients may have a higher kidney function at study entry or show a much faster CKD progression than others. This heterogeneity - in baseline eGFR, dropout and number of eGFR values between patients - should be taken into account when investigating risk factors associated with kidney function decline.

In the literature investigating changes in kidney function over time, two methods are commonly used: linear regression of individual slopes and linear mixed-effects models (LMMs). Both methods use repeated eGFR values within an individual over time. The methods differ in the way the overall GFR decline is estimated. In the linear regression method, individual eGFR declines or slopes are estimated, using linear regression based on at least two eGFR estimates over time. All values of a patient are collapsed into a single summarizing eGFR decline, yielding an individual eGFR slope for each patient. Subsequently a risk factor such as blood pressure is associated with this summarized decline rate using yet another linear regression with the individual slopes as outcome. By summarizing these individual eGFR declines, this method is not able to take account of the abovementioned heterogeneity in dropout, baseline kidney function values and number of eGFR values between individuals. A method that does take account of these sources of heterogeneity when analyzing eGFR trajectories is the LMM. LMMs, used for repeated measures designs, are a special case of multilevel or hierarchical linear models.[11]

The differences between the two methods, and the interpretation and use of an LMM are not always straightforward. Therefore, we aimed to highlight the differences between linear regression on individual slopes and LMMs when used for the purpose of estimating the eGFR

decline over time and its association with a certain risk factor. This will be illustrated by a clinical example of the effect of baseline diastolic blood pressure (DBP) on the decline of kidney function over time.

CLINICAL EXAMPLE: EFFECT OF DBP ON KIDNEY FUNCTION DECLINE

Study population

We used the prospective PREdialysis PAtient REcord-2 (PREPARE-2) cohort, described elsewhere in more detail.[12, 13] In summary, incident adult CKD 4-5 patients starting pre-dialysis care were included when referred to one of the 25 participating Dutch specialized pre-dialysis outpatient clinics (inclusion period 2004-11). Clinical and laboratory data were collected every 6 months. Patients were followed until start of dialysis, receiving a kidney transplant, death or censoring. Censoring was defined as recovery of kidney function prior the start of renal replacement therapy, refusal of further study participation, moving to an outpatient clinic not participating in the PREPARE-2 study, loss to follow-up, or 18 October 2016 (end of follow-up), whichever came first. The study was approved by the medical ethics committee or institutional review board (as appropriate) of all participating centers.

Study exposure and outcome

The study exposure in this illustrative example is baseline DBP. Baseline was defined as the first available measurement at cohort entry. DBP was dichotomized based on the median value of DBP, i.e. 80 mmHg. The study outcome was kidney function decline per year. Kidney function, based on serum creatinine levels, was estimated using the CKD-EPI equation.[14] Kidney function decline was estimated based on all available individual eGFR values during the first two years of pre-dialysis care. In patients initiating dialysis, eGFR values until 2 weeks before the start of dialysis were used, because eGFR values after this point in time were no longer representative for the actual kidney function.[13]

Analyses were performed with and without adjustment for potential baseline confounders: sex, age, race, smoking, alcohol use, primary kidney disease and co-morbidities cardiovascular disease (angina pectoris, coronary disease, and/or myocardial infarction) and diabetes. Statistical analyses were performed with SPSS Statistics 23 (IBM, Armonk, NY, USA).

Results using linear regression versus linear mixed-effects model

We used both linear regression on individual slopes and the LMM to investigate the association between baseline DBP and eGFR decline. We now demonstrate the differences in results obtained when using both methods. In Supplementary Materials 1 and 2, we provided equations and an example SPSS syntax for both linear regression on individuals slopes and the LMM, including general technical issues to keep in mind for modeling the LMM and an example how to interpret LMM results obtained in SPSS, using the example below.

Table 1 Association of diastolic blood pressure with decline in kidney function during the first two years of pre-dialysis

Diastolic blood pressure (mmHg)	N	Unadjusted additional change in eGFR decline (mL/min/1.73m²/ year)	Adjusted additional change in eGFR decline (mL/min/1.73m²/ year)[a]
Linear regression on individual slopes			
< 80	129	0	0
≥80	142	2.03 (1.43; 2.62)	2.05 (1.44; 2.66)
Linear mixed models on subjects for which linear regression on individual slopes was performed[b]			
< 80	129	0	0
≥80	142	1.65 (0.82; 2.49)	1.70 (0.90; 2.51)
Linear mixed models in total study population[b]			
< 80	202	0	0
≥80	214	1.80 (0.98; 2.63)	1.91 (1.12; 2.71)

[a]Adjusted for sex, age, race, smoking, alcohol use, primary kidney disease, and co-morbidities cardiovascular disease and diabetes.
[b]The fixed effects included time, baseline DBP and baseline DBP*time. For the adjusted results, confounders and the interaction terms for each confounder*time were added. A random intercept and slope model was used.

To estimate the eGFR decline, we use linear regression on individual slopes, for which at least two eGFR values within an individual over time are needed. In total, 271 patients of the study population had at least two eGFR values available and were included in the analysis. All results are shown in Table 1. For frequencies of different reasons of dropout after the two year follow-up period, see Supplementary Material 3. For categorical risk factors, it applies that the estimated effect is relative to a reference category. First, in the linear regression analysis, the adjusted additional change in eGFR decline is 2.05 [95% confidence interval (CI) 1.44-2.66) mL/min/1.73m^2 per year in patients with a DBP ≥80 mmHg compared to individuals with a DBP <80 mmHg, i.e. the reference category. In other words, patients with a DBP ≥80 mmHg on average have a 2.05 mL/min/1.73m^2 faster eGFR decline per year than patients with a DBP <80 mmHg, given a fixed sex, age, etcetera. Second, using the LMM, in the same study population, yielded an adjusted additional change in annual eGFR decline of 1.70 (95% CI: 0.90-2.51) mL/min/1.73m^2 in individuals with a DBP ≥80 mmHg compared to individuals with a DBP <80 mmHg.

Remarkably, this example shows that the obtained additional annual eGFR decline estimates are not the same when directly comparing the linear regression method to LMMs. How could this be explained and which is the better estimate? In the population of 271 patients, dropout was already at 22% after one year of follow-up. Could this dropout rate have influenced the results? Below, we will explain the underlying concepts and provide answers using this example.

Before discussing the differences between the two methods, an important strength of the LMM is that it allows us to also include individuals with only one eGFR value available during the follow-up period. Estimating the LMM in the extended sample of 416 patients, the adjusted additional annual kidney function decline was 1.91 (95% CI 1.12-2.71) mL/min/1.73m^2 for patients with a DBP ≥80 mmHg versus DBP <80 mmHg. Although in this particular case this estimate seems to be similar to those obtained in linear regression on individual slopes, we should not forget that the LMM uses the full sample, making use of all available information and thereby reducing the risk of selection bias. Of note, the wider 95% CIs are inherent to the use of LMMs, which we will touch upon below.

Underlying concepts of linear regression versus linear mixed-effects models

To obtain population-averaged eGFR declines in association to a risk factor (DBP), linear regression on individual slopes is a commonly used method. This is achieved in a two-stage approach.[15] In the first stage, individual slopes of kidney function over time are estimated, also called patient-specific regression coefficients. For this purpose, using all values of a single patient, a simple linear regression model is estimated with eGFR as outcome variable, defined as the kidney function estimated at different time points, and time as exposure, meaning the time between baseline and each time point at which the kidney function was estimated. This first stage is based on the assumption that the underlying eGFR trajectory is linear for each patient. The estimated slope of a patient represents the eGFR decline for a pre-specified time period; in our example, an annual eGFR decline (mL/min/1.73m^2/year). Thus, in this first step, all eGFR values of a patient are collapsed into a single summary measure, yielding one eGFR slope for each individual patient. In the second stage, a linear regression model is used in which these previously estimated slopes per individual are analyzed as outcome. In our example, this outcome variable (decline in eGFR) is related to baseline DBP (exposure). In aetiological research, we further adjust for potential confounders in this stage using a more elaborate model.[16]

Following the clinical example, clear differences in obtained eGFR decline are present using the two-stage linear regression approach versus LMMs. Linear regression on individual slopes

is quite simple and easy to understand. However, four important drawbacks exist. The solution for these drawbacks is provided by the LMM: the key characteristics of the LMM align with the problems encountered with aforementioned two-stage approach. The LMM retains all information and variability in the data when examining eGFR change over time. But how is the LMM able to do this? Below we discuss the four drawbacks of the two-stage linear regression approach and we provide the associated solutions using LMMs (Box 1).

Box 1. Differences between linear mixed-effects models and linear regression on individual models

- LMMs retain all information and variability in the data.
- Variability in different baseline eGFRs or eGFR slopes between individuals is taken into account by the LMM.
- LMMs take account of variation in number of eGFR values between individuals.
- LMMs deal accurately with dropout in longitudinal studies.
- In the LMM, individuals with only one eGFR value can be included to estimate the eGFR decline at population level.

Box 2. Fixed- and random-effects model in the LMM

1. The '*fixed-effects model*' contains the effects at population level. We aim to estimate the trajectory at population level, for instance the mean eGFR trajectory at population level, characterized by a population baseline value and slope.

2. The '*random-effects model*' may include
   - *Random intercepts model*
     The baseline eGFR value is also called the intercept and the LMM takes into account the variability in baseline eGFR values between individuals by defining a random intercepts model. For a given individual, the random intercept quantifies the difference between the observed baseline eGFR value of the individual and the population-averaged baseline eGFR value.
   - *Random slopes model*
     For a given individual, the random slope quantifies the difference between the observed eGFR slope of the individual and the population-averaged eGFR slope.

First, in linear regression on individual slopes, all eGFR values of a patient are collapsed into a single summary individual eGFR slope, as illustrated in Figure 1, which is then used as the outcome in the second stage. Consequently, the variability in the estimates of an individual, on which the eGFR slope is based, is not handled properly. In addition, the variability in baseline eGFR values between individuals is totally ignored by the linear regression model. The LMM provides a solution for these problems, because the LMM is able to take into account both the variability of baseline eGFR and eGFR slopes between patients (Figure 2). In general, we aim to estimate the trajectory at population level, for instance, the mean eGFR trajectory at population level, characterized by a population baseline value and slope. These are also called fixed effects (Box 2). However, an individual's eGFR trajectory could deviate from this mean eGFR trajectory in the overall study population. Due to variability around the population-averaged baseline eGFR, the baseline eGFR between individuals could vary. For instance, the overall population-averaged baseline eGFR could be 14 mL/min/1.73m^2, while a certain individual had a baseline eGFR value of 12 mL/min/1.73m^2. This difference is represented by Subject 1 compared to the population mean at time 0 in Figure 2. In addition, the eGFR slope of an individual over time could be the same as the population-averaged eGFR slope, just like in Subject 1 (i.e. 2 mL/min/1.73m^2/year), or could deviate from the population-averaged eGFR slope, as is the case for Subject 2 (i.e. 1 mL/min/1.73m^2/year). The individual deviations from the population level trajectory are quantified by defining the so-called random effects model (see Box 2 for more details). Because the model deals properly with the variability in baseline eGFR values and eGFR slopes, wider 95% CIs are inherent to the use of LMMs compared to linear regression on individual slopes, which ignores this variability. The change in time may not be necessary linear, i.e. the rate of decline is not necessarily constant in time. By forcing a linear trend, information could be lost. The LMM allows for modeling nonlinearities over time.

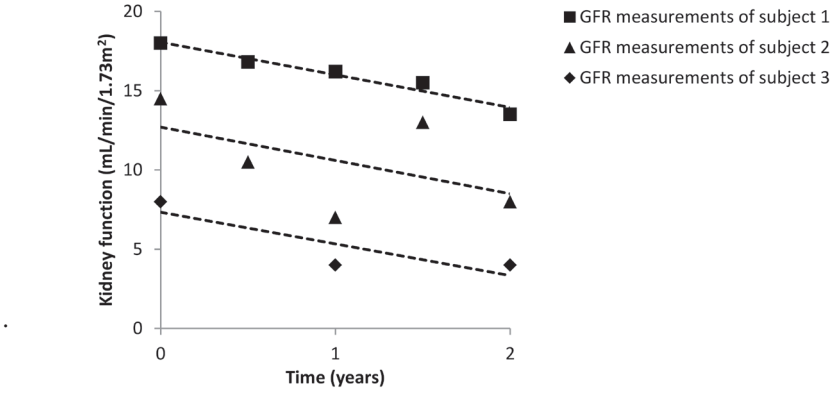

Figure 1. Illustration of the fitted line by linear regression on individual slopes during the first step of the two-stage approach. The dashed line is the line fitted by the linear regression model, based on available eGFR values for each subject. The individual slope for all subjects is 2 mL/min/1.73m^2/year despite the presence of different intercepts and the large heterogeneity in eGFR values between the subjects. Also the heterogeneity in available number of eGFR values is ignored. These issues are not taken into account by the linear regression model on individual slopes.

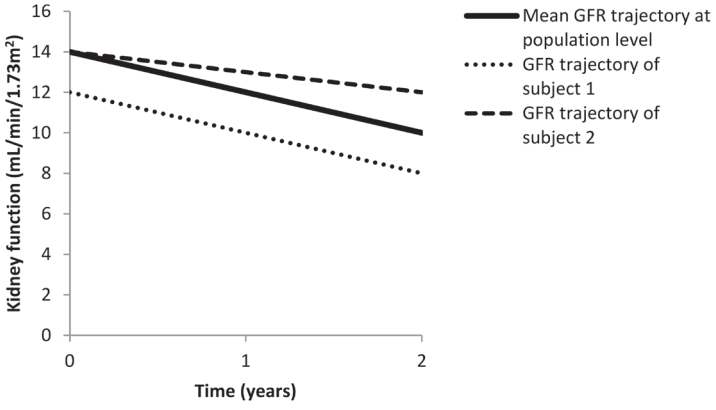

Figure 2. Illustration of LMM to model eGFR trajectories over time with a mixture of fixed and random effects. Fixed-effects model is represented by the population mean. Individuals baseline eGFR at time 0 of Subject 1 deviates from the population-averaged baseline eGFR, which is taken into account by the random intercepts model. The eGFR slope of Subject 2 deviates from the population-averaged eGFR slope and is taken into account by the random slopes model.

Second, using linear regression, estimated individual slopes might be accurate for patients with many repeated eGFR values available during the whole follow-up, but it will result in less accurate estimated slopes for patients with only a few values available. Again, the individual slopes in linear regression are obtained by fitting a straight line through all available eGFR values over time for each individual. In Figure 1, all subjects (Subjects 1-3) have the same

annual eGFR decline of 2 mL/min/1.73m^2 as estimated by the linear regression model. However, Subject 3 only has 3 eGFR measurements available compared to 5 eGFR values available for Subjects 1 and 2. All values are collapsed into one summarized eGFR decline, causing that the variability in the number of values between individuals is ignored. Importantly, the LMM takes this variation in number of eGFR values between individuals into account due to the fact that individuals with more eGFR values available contribute more to the overall population mean than individuals with less eGFR values available.

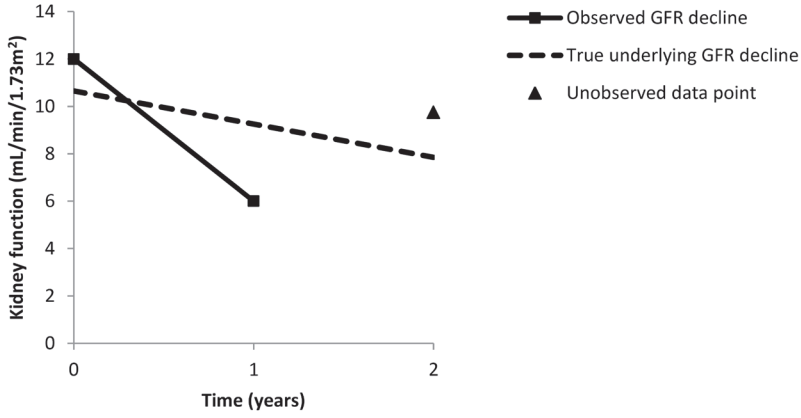

Figure 3. Illustration of the conceptual difference in dealing with dropout using linear regression on individual slopes and the LMM. Suppose an individual with dropout after 1 year and the illustrated eGFR values: the squared boxes are the observed eGFR values, with the second value randomly low compared to the true underlying eGFR decline. Due to the extrapolation of the observed eGFR slope from an individual after dropout by linear regression, the overall eGFR decline will be overestimated. The LMM is able to take the dropout into account and provides an eGFR decline closer to the true kidney function decline.

Third, linear regression does not take into account whether the follow-up period is ended earlier than intended due to dropout for a certain individual when estimating the population-averaged slope. Individual slopes in linear regression are obtained by fitting a straight line through all available eGFR values over time within each individual, ignoring whether follow-up was complete or not. When an individual drops out, the observed slope is extrapolated over the complete study period. This can result in biased estimates. For each individual observed, eGFR values could deviate from the true underlying eGFR value due to random measurement errors or random noise. In general, some of the observed eGFR values are higher or lower than the true eGFR value (Figure 3). In addition, repeated eGFR values could be missing for several reasons. The reasons for missing data are formally described by the missing data mechanism. In practice, three mechanisms can be distinguished: missing completely at random (MCAR), missing

at random (MAR), and missing not at random (MNAR).[17-19] MCAR applies when missingness is unrelated with the outcome of interest, e.g. relocation or device malfunction. In this case the observed data are a random sample of the target population and unbiased estimates can be obtained even when using linear regression on individual slopes. However, such a mechanism is hardly likely to hold in practice. Instead MAR is more realistic to apply in practice. Under MAR the reason for dropout is related to previously observed eGFR values. In this case, the observed data cannot be considered as a random sample from the target population anymore. Thus the use of linear regression on individual slopes will lead to biased estimates. In contrast, unbiased estimates are obtained using LMMs. Especially when the observed eGFR value is lower than the true eGFR value, the estimated kidney function decline will be overestimated using linear regression on individual slopes. This is reflected in a frequent clinical scenario where the observed low eGFR value could be a reason for starting renal replacement therapy and thus for dropout of a patient from the study (based on previously observed eGFR values). Importantly, instead of extrapolating individual slopes based only on measurements of that individual, the LMM estimates the individual slope also based on complete observed data of other similar individuals in the dataset. In this way, the LMM is able to take the dropout into account. The anticipated result of using LMMs is that an overall eGFR decline at population level is obtained closer to the true eGFR slope than linear regression. In longitudinal studies with high dropout rates, especially early in follow-up, LMMs will provide more accurate eGFR declines than linear regression.[20, 21] This is reflected in our example: the adjusted additional change in annual eGFR decline was 2.05 (95% CI 1.44-2.66) for individuals with a DBP ≥80 mmHg compared to individuals with a DBP <80 mmHg and 1.70 (95% CI 0.90-2.51) mL/min/1.73m^2 using the two-stage linear regression approach and the LMM, respectively. Clearly, in this example, the obtained additional annual eGFR decline is overestimated using linear regression, due to a dropout of 22% after one year. The last possible missing data mechanism, MNAR, applies when the reason for dropout is related to unobserved eGFR values, e.g. patient is lost to follow-up due to an improvement or deterioration of her condition which we never got the chance to measure. In this case, neither the linear regression on individual slopes nor the LMMs will provide valid results. More sophisticated methods of analysis are required in this case.[22] However, this mechanism is unlikely to hold in clinical practice.

Fourth, as we saw in the example above using linear regression, an individual slope could only be estimated in the presence of at least two eGFR values. Patients with only one eGFR value available are therefore excluded from the analysis.[23] However, these values could also contribute to a better estimation of the intercept of the fitted line, which represents the eGFR

decline. The omission of these values will reduce the sample size for the analysis and may introduce selection bias. Selection bias in linear regression on individual slopes could lead to either an overestimation or underestimation of the true underlying kidney function decline. An overestimation could occur when patients with at least two eGFR values have a worse prognosis, as reason that eGFR is more often estimated, than patients with one eGFR value. In contrast, an underestimation could occur when the former patients have a better prognosis and if, for instance, patients with only one eGFR value died prior to the next eGFR value. However, using the LMM allows us to include also those patients with only one eGFR value available. Thereby fully using the sample size and eliminating selection bias for estimating the eGFR trajectory over time at population level. In our example, this resulted in the inclusion of 416 patients instead of 271 patients. Coincidentally, the obtained results are closer together using linear regression on individual slopes in 271 patients compared to LMMs in 416 patients, but of course we have to keep in mind that linear regression only includes a subgroup of the study population used in the LMM. Of note, the results based on the LMM in the full sample of 416 patients and the linear regression on individual slopes in 271 patients should not be compared. If linear regression could be performed in the full sample of 416 patients, an even higher additional change in eGFR decline than 2.05 mL/min/1.73m^2/year would likely have been obtained, however it is impossible to estimate this.

CONCLUSIONS

We aimed at creating awareness for the distinction between the LMM and linear regression analysis on individual slopes for the purpose of estimating the kidney function decline over time. The LMM is the preferred and recommended model for research questions regarding eGFR trajectories over time at population level. Dropouts and heterogeneity in number of eGFR values between individuals are accurately handled by LMMs. Also, individual differences in both baseline eGFR and eGFR slopes are taken into account by the fixed and random effects in LMMs.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1: Equations and SPSS syntax for linear regression on individual slopes

1.1. Equations

1. First stage of two-stage approach:

For each patient i the following linear regression model will be estimated:

$eGFR_{ij} = A_i + \beta_i t_{ij} + \varepsilon_{ij}$

$eGFR_{ij}$ = the eGFR value of patient i at time t_{ij}
A_i = the intercept, i.e. the expected value of eGFR at baseline for patient i.
β_i = the slope of eGFR for patient i, i.e. his/her average annual change in GFR.
t_{ij} = the time (in years) of visit j for patient i.
$A_i + B_i t_{ij}$ provides the expected value of eGFR for patient i at time t_{ij}
ε_{ij} = a random deviation of the expected value of eGFR at time t_{ij}

2. Second stage of two-stage approach:

All individual estimated slopes (B_i) derived from the first stage will be used to estimate the following linear regression model:

$B_i = \gamma_0 + \gamma_1 high + \mu_i$

γ_0 = intercept; the mean (population-averaged) eGFR slope in patients with DBP < 80 mmHg at baseline.
γ_1 = for the categorical variable: the mean (population-averaged) difference in eGFR slopes between patients with DBP < 80 mmHg versus ≥ 80 at baseline μ_i = random variation of patient i about the mean (population-averaged) eGFR slope

1.2. Example of SPSS syntax

First, an example of a fictional dataset in long format with the study numbers, baseline exposure, time-varying outcome and baseline confounders:

	studynumber	eGFR_epi	Time	categorical_DBP	smoking	CVD	age	DM	PKD
1	1	14,34	,00	1,00	0	0	42,25	1,00	3,00
2	2	8,84	,00	,00	1	1	44,77	,00	2,00
3	2	7,82	,61	,00	1	1	44,77	,00	2,00
4	2	9,79	1,05	,00	1	1	44,77	,00	2,00
5	3	19,36	,00	1,00	1	0	68,79	1,00	4,00
6	3	17,47	1,16	1,00	1	0	68,79	1,00	4,00

First stage of two stage approach of linear regression on individual slopes:

Individual slope extraction via Output Management System (OMS)[11]

```
SORT CASES BY studynumber.
SPLIT FILE LAYERED BY studynumber.
DATASET DECLARE GFR_SLOPES.

OMS
 /SELECT TABLES
 /IF COMMANDS=['Regression'] SUBTYPES=['Coefficients']
 /DESTINATION FORMAT =SAV
  OUTFILE = GFR_SLOPES.
REGRESSION
 /MISSING listwise
 /STATISTICS coeff outs r anova
 /CRITERIA=PIN(0.05) POUT(.10)
 /NOORIGIN
 /dependent eGFR_epi
 /METHOD=enter Time.

OMSEND.
SPLIT FILE off.

CASESTOVARS
  /ID=studynumber
  /GROUPBY=VARIABLE.

DATASET ACTIVATE GFR_SLOPES.
SORT CASES BY studynumber.
```

eGFR_epi are the eGFR values over time based on the CKD-EPI equation. The variable *Time* represents the time between the index date and each subsequent eGFR value.

Second stage of two-stage approach:

We obtained individual slopes and we incorporated these in the unadjusted and adjusted linear regression models. Therefore, the original datafile first has to be matched with the file with obtained GFR_SLOPES, including the individual_slopes variable.

```
MATCH FILES /FILE=*original datafile*
  /FILE='GFR_SLOPES'
  /BY studynr.
EXECUTE.
```

Unadjusted model for the association between categorical DBP and subsequent kidney function decline:

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT individual_slopes
  /METHOD=ENTER categoricalDBP.
```

categoricalDBP represents the categorical diastolic blood pressure ≥80 mmHg and <80 mmHg at baseline.

Adjusted model for the association between categorical DBP and subsequent kidney function decline:

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT individual_slopes
  /METHOD=ENTER categoricalDBP sex age race smoking alcohol PKD CVD DM.
```

"sex age race smoking alcohol PKD CVD DM" represent the confounders sex, age, ethnicity, smoking alcohol use, primary kidney disease, cardiovascular disease and diabetes, respectively.

1.3. SPSS output of linear regression on individual slopes

Unadjusted model for the association between dichotomized DBP and subsequent kidney function decline:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-1,089	,220		-4,941	,000	-1,521	-,656
	categoricalDBP	-2,026	,305	-,230	-6,647	,000	-2,625	-1,428

a. Dependent Variable: Individual_slopes: Unstandardized Coefficients B

Adjusted model for the association between categorical DBP (≥80 mmHg and <80 mmHg) and subsequent kidney function decline:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-4,760	1,482		-3,212	,001	-7,670	-1,851
	categoricalDBP	-2,048	,310	-,243	-6,615	,000	-2,656	-1,440
	sex	,764	,338	,083	2,261	,024	,101	1,427
	age	-6,465E-5	,011	,000	-,006	,995	-,022	,022
	race	-,640	,307	-,077	-2,083	,038	-1,244	-,037
	smoking	1,491	,412	,130	3,619	,000	,682	2,300
	alcohol	,218	,315	,026	,693	,489	-,400	,837
	PKD	,015	,178	,004	,084	,933	-,334	,364
	CVD	,121	,325	,014	,372	,710	-,517	,759
	DM	,254	,438	,026	,580	,562	-,606	1,114

a. Dependent Variable: Individual_slopes: Unstandardized Coefficients B

For both models, the additional annual eGFR decline in individuals with a DBP ≥80 mmHg compared to individuals with a DBP <80 mmHg are presented in red, including the associated 95% confidence intervals. These numbers correspond to the results described in **Table 1**.

Supplementary Material 2: Equations and SPSS syntax for linear mixed-effects models

2.1. General technical issues for modeling and interpreting the LMM

There are several issues to keep in mind when modeling the LMM. First, we need to think about the exposure, outcome and time variable. In the current example, baseline DBP is the exposure and the eGFR trajectory per year (time period) is the outcome of interest. Second, the fixed effects should be specified in the LMM by including the exposure (DBP) and time separately, in addition to the interaction term of exposure with time (DBP*time). We included the interaction term of the baseline independent variable (DBP) with time, because we are interested in the baseline effect of DBP on kidney function decline over time. This interaction term allows that the effect of baseline DBP on the eGFR value is different over time, i.e. across the years. In other words, with this interaction term the effect of the baseline DBP on the eGFR slope is obtained, see also Supplemental Figure 1 (Supplementary Material 2.4). When estimating the adjusted effects instead of unadjusted effects, the confounder, the time variable, and the interaction term between confounder and time are included. This is applicable for each confounder included in the model. The interaction term is crucial to add into the model, because the effect of baseline DBP on subsequent eGFR decline could be affected by baseline confounders over time. Third, besides specifying the fixed effects, we need to specify the patient-specific part using random effects. To take account of both variation in individuals baseline eGFR (intercept) and eGFR slope compared to the population-averaged intercept and slope, we specified the random intercept and slope model in the LMM. As an example, Supplementary Material 2.2 displays the associated SPSS syntax and underlying equations. Fourth, often an 'unstructured' covariance matrix is used for the random effects, which is the most flexible covariance matrix. Fifth, the final model should be fitted with the restricted maximum likelihood (REML) method.[1]

How should we interpret the generated output of an LMM? For categorical risk factors applies that the estimated effect is relative to a reference category. Note that the output of standard software displays regression coefficients for every term included in the model. When interpreting the unadjusted effect of baseline DBP on subsequent kidney function decline over time, the interaction term of baseline DBP with time is the term of interest. When interpreting the adjusted effects of baseline DBP on subsequent kidney function decline, also the interaction of the baseline exposure with time should be interpreted, given baseline confounders are fixed.

[1] FitzMaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. John Wiley & Sons, Hoboken, NJ: 2004; 99-102

2.2. Equations

The following equation belongs to the linear mixed-effects model expressing the observed GFR value for a patient i at visit j with a given diastolic blood pressure (=unadjusted model):

$$eGFR_{ij} = (\beta_0 + \boldsymbol{\mu_{0i}}) + \beta_1 high + (\beta_2 + \boldsymbol{\mu_{1i}})t_{ij} + \beta_3 high*t_{ij} + \varepsilon_{ij}$$

β_0 = the mean (population-averaged) baseline eGFR in patients.
β_1 = the mean (population-averaged) difference in eGFR at baseline between patients with DBP < 80 mmHg versus DBP ≥80 mmHg at baseline.
β_2 = the mean (population-averaged) slope of eGFR in patients with DBP < 80 mmHg at baseline.
β_3 = the mean (population-averaged) difference in eGFR slopes between patients with DBP < 80 mmHg versus DBP ≥80 mmHg at baseline.

$\boldsymbol{\mu_{0i}}$ = represents random intercept model, i.e. a random deviation of patient i from the population-averaged baseline eGFR in patients with identical baseline characteristics
$\boldsymbol{\mu_{1i}}$ = represents random slope model, i.e. a random deviation of patient i from the population-averaged eGFR slope, i.e. β_2 for patients with DBP <80 mmHg; $\beta_2 + \beta_3$ for patients with DBP ≥80 mmHg at baseline.
ε_{ij} = random error at time t_{ij}

The general equation for an adjusted linear mixed model expressing the observed eGFR value at visit j for patient i with a given baseline DBP, age, sex (and other confounders) is given by the equation:

$$eGFR_{ij} = (\beta_0 + \boldsymbol{\mu_{0i}}) + \beta_1 high + (\beta_2 + \boldsymbol{\mu_{1i}})t_{ij} + \beta_3 high*t_{ij} + \underline{\beta_4 age_i + \beta_4 age_i*t_{ij} + \beta_5 sex_i + \beta_5 sex_i*t_{ij} + \beta_{ni} + \beta_{ni}*t_{ij} + \varepsilon_{ij}}$$

The underlined text represents an adjusted model with confounders. All the fixed effects β could now be interpreted as above for patients with DBP < 80 mmHg versus DBP ≥80 mmHg, with fixed age, sex etcetera (remaining confounders) at baseline.

2.3. Example of SPSS syntax

Below we describe the unadjusted model for the association between the categorical baseline DBP and subsequent kidney function decline. The categorical DBP variable should be incorporated behind the BY in the LMM.

MIXED eGFR_epi with *Time BY categoricalDBP*
/criteria=cin(95) MXITER(1000)
*/fixed=Time categoricalDBP categoricalDBP*Time*
/random=intercept Time | subject (studynumber) covtype(un)
/method=reml
/print=solution.

eGFR_epi are the eGFR values over time based on the CKD-EPI equation. The variable *Time* represents the time between the index date and each subsequent eGFR value. *categoricalDBP* represents the dichotomized diastolic blood pressure ≥80 mmHg and <80 mmHg at baseline. For the fixed effects, we included DBP at baseline and the time and the interaction between DBP at baseline and the time. With *"random=intercept Time"* the random intercept and slope model is defined and the "unstructured" covariance matrix is defined with *covtype(un)*. The model is fitted using the restricted maximum likelihood (*reml*) method.

When defining the adjusted model for the association between categorical baseline DBP and subsequent kidney function decline, all categorical confounders should be placed behind the BY in the model. Furthermore, in addition to the baseline confounders, the interaction between baseline confounder and time is added in the fixed effects part.

MIXED eGFR_epi WITH *Time BY categoricalDBP age sex race smoking alcohol PKD CVD DM*

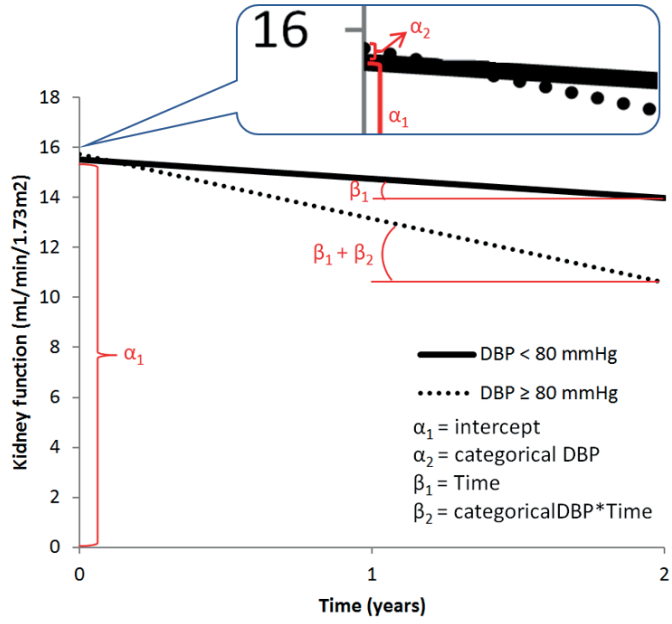
/criteria=cin(95) MXITER(1000)
/fixed=Time categoricalDBP categoricalDBP*Time sex age race smoking alcohol PKD CVD DM age*Time DM*Time CVD*Time smoking*Time race*Time sex*Time PKD*Time alcohol*Time
/random=intercept Time | subject (studynumber) covtype(un)
/method=reml
/print=solution.

2.4. Interpretation SPSS Output of a linear mixed-effects model

SPSS Output Linear Mixed-Effects Model

Parameter	Estimate	Std. Error	Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept = α_1	15,525501	,417406	,000	14,704857	16,346144
Time = β_1	-,767143	,297844	,011	-1,354457	-,179828
[categoricalDBP≥80] = α_2	,200995	,580159	,729	-,939655	1,341645
[categoricalDBP<80]	0	0	.	.	.
[categoricalDBP≥80] *Time = β_2	-1,804733	,416824	,000	-2,626688	-,982777
[categoricalDBP<80] *Time	0	0	.	.	.

a. Dependent Variable: eGFR_epi.



Supplemental Figure 1. Interpretation of SPSS output for the unadjusted association between baseline DBP and kidney function decline over time using the linear mixed-effects model. The interpretation of the SPSS output is illustrated according to a figure, in which the intercepts (α) and slopes (β) for the association between baseline DBP (<80 versus ≥80 mmHg) are explained. α_1 is the intercept for DBP <80 mmHg (=reference category); $\alpha_1+\alpha_2$ is intercept for DBP ≥80 mmHg; β_1 is the slope for DBP <80 mmHg; $\beta_1+\beta_2$ is the slope for DBP ≥80 mmHg.

Supplementary Material 3: Reasons of dropout

After two years of follow-up a total of 114 patients dropped out the study due to different reasons, see the table below. This equals to a total dropout rate of 42% from a total of 271 patients.

Reasons of dropout	Frequencies (%)
Dialysis initiation	4 (3.5)
Kidney transplant	32 (28.1)
Death	24 (21.1)
Recovery of kidney function prior the start of renal replacement therapy	15 (13.2)
Refusal of further study participation	12 (10.5)
Moving to an outpatient clinic not participating in the PREPARE-2 study	3 (2.6)
Loss to follow-up	3 (2.6)
End of follow-up (October 18, 2016)	21 (18.4)
Total	**114**

CHAPTER 5

KIDNEY FUNCTION AND SYMPTOM DEVELOPMENT OVER TIME IN ELDERLY PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE: RESULTS OF THE EQUAL COHORT STUDY

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ABSTRACT

Background: Initiation of renal replacement therapy often results from a combination of kidney function deterioration and symptoms related to chronic kidney disease (CKD) progression. We investigated the association between kidney function decline and symptom development in patients with advanced CKD.

Methods: In the EQUAL study, a European prospective cohort study, patients with advanced CKD of ≥65 years and a kidney function that dropped below 20 mL/min/1.73m^2 were followed for one year. Linear mixed effects models were used to assess the association between kidney function decline and symptom development. The sum score for symptom number ranged from 0-33 and for overall symptom severity from 0-165, using the Dialysis Symptom Index.

Results: At least one kidney function estimate with symptom number or overall symptom severity was available for 1109 and 1019 patients, respectively. The mean (95%-confidence interval) annual kidney function decline was 1.70 (1.32; 2.08) mL/min/1.73m^2. Mean overall increase in symptom number and severity was 0.73 (0.28; 1.19) and 2.93 (1.34; 4.52) per year, respectively. A cross-sectional association between level of kidney function and symptoms was lacking. Furthermore, kidney function at cohort entry was not associated with symptom development. However, each mL/min/1.73m^2 of annual kidney function decline was associated with an extra annual increase of 0.23 (0.07; 0.39) in the number of symptoms and 0.87 (0.35; 1.40) in overall symptom severity.

Conclusions: A faster kidney function decline was associated with a steeper increase in both symptom number and severity. Considering the modest association, our results seem to suggest that repeated thorough assessment of symptom development during outpatient clinic visits, in addition to the monitoring of kidney function decline, is important for clinical decision-making.

INTRODUCTION

Patients with advanced stage chronic kidney disease (CKD) suffer from a wide range of symptoms. A growing body of evidence exists that CKD symptom burden is negatively correlated with health-related quality of life, and positively correlated with increased morbidity and mortality rates.[1, 2] Previous studies in people with stage 4-5 CKD show that poor mobility and weakness is experienced by more than two thirds of the patients, while poor appetite, pain, and itching is reported in about 60%.[3] In number of symptoms and severity, patients with CKD stage 5, managed conservatively, experienced a symptom burden similar to that of an advanced cancer population.[4] In general, the more prevalent symptoms were rated as more burdensome. However, the symptom pain was an exception, for which a disproportionately greater severity was reported.[4] Patients rate symptoms as one of the most important aspects of their kidney disease. One of the main reasons behind this is the severity of symptoms they experience.[5] Healthcare providers and patients also believe that symptoms should be one of the main focuses in CKD research.[6, 7]

In a medical speciality like rheumatology decision-making often involves evaluation of symptom burden. As an example, the disease activity score, including symptoms, is used in decision-making regarding treatment initiation but also to evaluate the effect of treatment. Also in clinical nephrology, there is a fundamental knowledge that symptom evaluation is important. KDIGO guidelines recommend the initiation of RRT when symptoms are present, which is often although not invariably in the glomerular filtration rate (GFR) range between 5 and 10 mL/min/m^2.[8] From a clinical point of view, it could be expected that symptoms increase while kidney function deteriorates in patients with CKD. Surprisingly, however, evidence for this association is lacking. This is important, as in general there is a lack of association between kidney function and symptoms in cross-sectional studies.[3, 9, 10] The interplay between kidney function and symptoms remains unclear for the question when to start dialysis, as also illustrated by the Initiating Dialysis Early And Late (IDEAL) study, where patients were randomized to an early versus late start dialysis based upon estimated GFR (eGFR).[11] In this study physical symptoms played an important role in deciding if and when to initiate dialysis. A large proportion of patients randomized to the late starting group started earlier due to the presence of uremic symptoms. Thus, even though symptom burden was demonstrated to play a major role in the decision-making for dialysis initiation in the IDEAL study, the longitudinal association between change in kidney function and change in symptoms over time in patients with advanced CKD was never empirically investigated.

To fill this gap, we aimed to study the association between kidney function decline and symptom development (i.e. symptom number and severity) over time in patients with advanced CKD. To replicate findings of existing literature, we also studied the cross-sectional association between level of kidney function and symptoms at baseline, and to expand on this, we explored the association between the level of kidney function and symptom development.

MATERIALS AND METHODS

Study design and population

The European Quality study on treatment in advanced chronic kidney disease (EQUAL study) is an ongoing prospective cohort study in patients with advanced CKD in Germany, Italy, Poland, Sweden, the United Kingdom, and the Netherlands. Approval was obtained from the medical ethical committees or corresponding institutional review boards (as appropriate) for all participating centers. All included patients gave their written informed consent. A full description of the EQUAL study has been published elsewhere.[12] In short, patients of ≥ 65 years were included with an incident estimated GFR (eGFR) drop to or below 20 mL/min/1.73m^2 in the last six months. Patients were eligible when followed in a nephrology clinic, and were excluded when the eGFR drop was the result of an acute event or when a history of RRT (i.e. start of dialysis, or kidney transplantation) was present. Identified patients who met the eligibility criteria were consecutively approached. Patients were followed until kidney transplantation, death, moving to a center not participating in the EQUAL study, refusal for further participation, loss to follow-up or end of follow-up, whichever came first. For the current analyses, the follow-up time would end at the first occurrence of January 2018 or initiation of dialysis. Follow-up data at cohort entry, after six and twelve months of follow-up were used from patients recruited between March 2012 and January 2018 and who filled out at least the symptom part of the patient questionnaire.

Data collection and variable definitions

In the EQUAL study patients are followed while receiving routine medical care as provided by the nephrology clinics. Data were collected and entered into a web-based clinical record form, developed for this specific purpose. Collected information included patients' demographics, primary kidney disease, comorbid condition, ethnicity, medication, diet, physical examination and laboratory data. Physical examinations and collection of laboratory data were performed according to standard protocols and procedures following the routine care at the local participating sites. For the uniformity of the data, all participating centers completed

a questionnaire capturing details on local laboratory methods, units of measurement and reference ranges. Subsequently, all data were recalculated into one uniform unit of choice. Kidney function was estimated according to the the 4-variable Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, race, and serum creatinine.[13] See Supplemental Table S1 for detailed variable descriptions of primary kidney disease, educational level, diabetes mellitus and psychiatric disease.

Data on lifestyle, marital status, and number and symptom severity were obtained through self-administered paper questionnaires. The list of symptoms (Supplemental Table S1) composed the original validated Dialysis Symptom Index (DSI) and complemented with items assessing the following symptoms: bleeding, loss of weight, and loss of strength.[14] These symptoms were added based on expert opinion of nephrologists collaborating on the EQUAL study. Furthermore, these symptoms were added at the bottom of the original DSI, thus did not influence the validity of the questionnaire. Patients responded about whether these symptoms were present in the past month. In total 33 symptoms were assessed, thus the total sum score for symptom number ranged from 0 to 33 symptoms. Additionally, for each symptom scored 'present', patients also rated symptom severity (how much burden they experienced) on a 5-point Likert scale ranging from 1 'not at all' to 5 'very much' burdensome. An overall symptom severity sum score ranging from 0 to 165 was generated, assigning a score of zero for symptoms that were absent.[15]

Statistical analyses

Baseline characteristics were presented as mean with standard deviation (SD) for normally distributed continuous variables, as median with interquartile range (IQR) for skewed continuous variables, and as frequencies with percentages for categorical variables.

For the main analyses, patients were included when at least one observation of both kidney function and symptom score was available. For the cross-sectional analysis, this applied at baseline and for the longitudinal analysis this applied for one observation in the 1 year of follow-up. Using linear mixed models only one observation is needed.[16] As a result, different patient numbers were used in the analyses (see Figure 1).

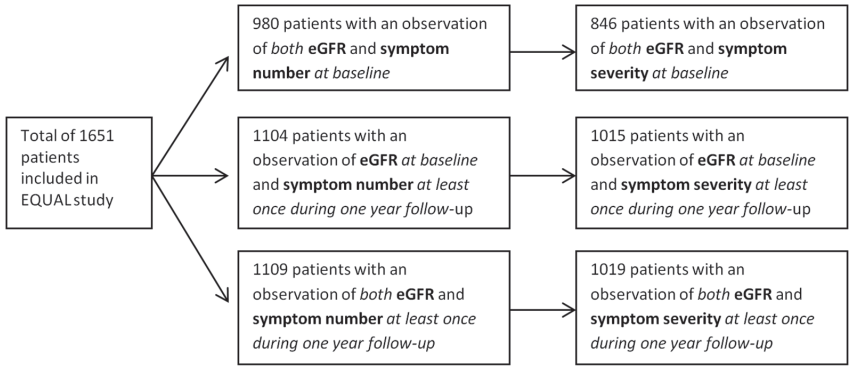

Figure 1. Flowchart of patient inclusion for the present analyses, based on data availability.

We performed three main analyses. Firstly, linear regression analysis was performed to estimate the cross-sectional association between the level of eGFR at baseline and both the number and severity of symptoms at baseline to replicate findings of existing studies.

Secondly, to investigate the association between the level of eGFR at baseline and the development in symptom number and severity over time, we used linear mixed effects models where patients were included as random intercepts and reported coefficient for the interaction between a continuous time and the level of eGFR at baseline.[16]

Thirdly, the longitudinal association between eGFR decline and the development of symptom burden (either the number or severity of symptoms) over time was also estimated using linear mixed effects models. Regression coefficients for the additional change in symptom burden with one unit change in GFR were obtained as outcome by modelling trajectories of kidney function and symptoms simultaneously, thereby allowing within and between individual variations using the fixed and random effects model. Correlations and standard errors were estimated using the delta method.[17]

Multiple imputation was used to minimize the risk of bias due to missing data.[18] Estimates and standard errors were calculated in each imputation set and pooled into one overall estimate and standard error according to Rubin's rules.[19, 20] All confounders were assumed to be missing at random for which multiple imputation using a fully conditional specification with 10 repetitions is a valid technique and reduces bias compared to complete case analysis.[21, 22] Exposure and outcome variables were not imputed. In the multiple imputation model, we included all potential confounders, exposure and outcome variables. Non-normally distributed variables were transformed to approximate normality before imputation and then the imputed values were transformed back to the original scale.[21]

All aforementioned analyses were adjusted for age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, body mass index (BMI), primary kidney disease, hemoglobin and proteinuria. For all analyses, the baseline confounders were used to adjust for confounding. In all aforementioned analyses, causal interpretations should be avoided.[23]

For the purpose of illustration, mean trajectories of kidney function decline and development in number and severity of symptoms are plotted in figures using estimated marginal (EM) means obtained from linear mixed models with a random intercept for each patient, including time as categorical variable at baseline, after 6 and 12 months of follow-up.

Sensitivity analyses

Several preplanned sensitivity analyses were performed to assess the robustness of our main results. Analyses were repeated using eGFR based on the CKD-EPI equation instead of the MDRD. The cross-sectional association between kidney function and symptoms was also assessed after 6 and 12 months of follow-up, to allow for more variability in eGFR. Furthermore, the longitudinal analyses regarding the association between kidney function level and symptom development, and the association between the kidney function and symptom trajectories, were repeated using a two-stage approach in linear regression analysis.[24] First, we calculated the individual linear regression slopes of change in symptoms and kidney function per patient. In the second stage we correlated either the baseline eGFR or individual eGFR declines with the calculated individual slopes of either symptom number or overall symptom severity in a linear regression model. Finally, analyses were repeated for 13 uraemia- or disease-related symptoms (see Supplemental Table S1). These 13 symptoms are an adapted list of symptoms based on symptoms reported by the KDOQI guidelines and reported as most prevalent, frequent or severe in advanced kidney failure in literature.[3, 9, 15, 25-29]

Analyses using linear mixed effects models were performed using SAS statistical package (version 9.4, SAS Institute, Cary, NC). All other analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, IL).

RESULTS

Baseline characteristics

For the present analyses, a total of 1109 patients were included with at least one observation of symptom number and eGFR-MDRD, and 1019 patients were included with at least one observation of overall symptom severity and eGFR-MDRD. Median (IQR) follow-up time was 0.98 (0.64; 1.03) year. Baseline characteristics of both patient groups are presented in Table 1. The mean (SD) baseline eGFR was 18.9 (5.4) and 18.8 (5.3) mL/min/1.73m^2 in those patients with scores on either the number or overall severity of symptoms available, respectively. The median (IQR) age was 75.9 (70.5-80.8) and 75.7 (70.2-80.5) years for patients with symptom number and symptom severity scores available, respectively. The symptoms muscle soreness, difficulty concentrating, constipation and decreased appetite increased the most in terms of reported symptom presence over the one year follow-up period in our study population (see Supplemental Figure S1). The symptom severity increased the most for the symptoms difficulty in becoming sexually aroused, muscle soreness, difficulty concentrating and decreased interest (see Supplemental Figure S2).

Baseline characteristics of patients with no observations of both eGFR-MDRD and overall symptom score during the first year of pre-dialysis care are shown in Supplemental Table S2. The baseline characteristics of included and excluded patients were comparable, though included patients comprised a slightly higher percentage of males than excluded patients. In the total EQUAL study population of 1651 patients, 205 patients initiated dialysis and 168 patients dropped out during the first year of follow-up, and 239 patients did not yet reach the end of the first year follow-up period.

Table 1. Baseline characteristics in patients with at least two visits with eGFR-MDRD and overall symptom score available during first year of pre-dialysis

	Symptom number and eGFR-MDRD available for at least one visit during one year pre-dialysis (N= 1109)[a]	Symptom severity and eGFR-MDRD available for at least one visit during one year pre-dialysis (N= 1019)[b]
Sex, male	764 (68.9)	698 (68.5)
Age, years	75.9 (70.5-80.8)	75.7 (70.2-80.5)
Ethnicity		
Caucasian	1087 (98.4)	1000 (98.4)
Black	6 (0.5)	6 (0.6)
Other	12 (1.1)	10 (1.0)
Primary Kidney Disease		
Glomerular disease	106 (9.6)	99 (9.7)
Tubulo-interstitial disease	95 (8.6)	89 (8.7)
Diabetes Mellitus	214 (19.3)	187 (18.4)
Hypertension	385 (34.7)	361 (35.4)
Other/ unknown	309 (27.9)	283 (27.8)
Educational level [c]		
No	27 (2.5)	24 (2.4)
Low	308 (28.8)	266 (27.0)
Intermediate	544 (50.9)	510 (51.8)
High	154 (14.4)	151 (15.3)
Other	36 (3.4)	34 (3.5)
Marital status, married or living together	714 (66.0)	662 (66.6)
Diabetes Mellitus, yes [d]	449 (41.3)	404 (40.4)
Hypertension, yes [e]	991 (92.2)	919 (92.6)
Cerebrovascular Disease, yes	168 (15.5)	152 (15.3)
Myocardial Infarction, yes	202 (18.5)	185 (18.5)
Malignancy, yes	228 (21.2)	210 (21.1)
Psychiatric disease, yes	86 (7.9)	75 (7.5)
Body Mass Index, kg/m²	28.2 (±5.3)	28.2 (±5.3)
eGFR baseline, ml/min/1.73m²	18.9 (±5.4)	18.8 (±5.3)
Serum albumin, g/L	37.6 (±5.9)	37.6 (±5.8)
Hemoglobin, mmol/L	7.2 (±0.9)	7.2 (±0.9)
Proteinuria, g/24h	1.5 (0.5-5.0)	1.5 (0.5-5.4)

Values are given as frequency (percentage), mean (±SD) or median (IQR), as appropriate.
[a] Missings: 0.4% ethnicity, 0.9% educational level, 2.5% marital status, 1.9% diabetes, 3.1% hypertension, 2.4% cerebrovascular disease, 1.8% myocardial infarction, 2.8% malignancy, 2.3% psychiatric disease, 6.6% BMI, 9.8% albumin, 2.1% hemoglobin, 71.8% proteinuria. [b] Missings: 0.3% ethnicity, 2.5% marital status, 3.3% educational level, 1.9% diabetes, 2.6% hypertension, 2.3% cerebrovascular disease, 1.8% myocardial infarction, 2.4% malignancy, 2.2% psychiatric disease, 6.8% BMI, 9.7% albumin, 2.1% hemoglobin, 71.9% proteinuria. [c] Defined as: low, no education or primary school only; intermediate, primary and secondary school; high, academic education. [d] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus, both type I and type II. [e] Defined as either the presence of hypertension as primary kidney disease or a history of hypertension.

Cross-sectional association of kidney function and symptoms at baseline

At cohort entry, there was no cross-sectional association between the level of kidney function and number of symptoms (Table 2). Furthermore, we found no association between the level of kidney function and overall severity of symptoms at baseline.

Table 2. Cross-sectional effect per unit lower eGFR-MDRD on symptom number and severity at baseline

	Symptom number (N=980)	Symptom severity (N=846)
Unadjusted	-0.01 (-0.08; 0.07)	-0.06 (-0.34; 0.23)
Adjusted [a]	0.004 (-0.07; 0.08)	0.06 (-0.22; 0.34)

[a]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at each specific time point (baseline, 6 or 12 months after cohort entry).

Association of kidney function at baseline and symptom development

No association was found between the level of kidney function at cohort entry and development of symptoms over time. This applied to both the number and overall severity of symptoms in the unadjusted and adjusted analysis (Table 3).

Table 3. Effect per unit lower eGFR-MDRD at baseline on annual change in symptom number and severity

	Symptom number (N=1104)	Symptom severity (N=1015)
Mean annual increase (95%-CI)	0.76 (0.30; 1.21)*	3.00 (1.41; 4.59)*
Extra increase per unit[a] lower kidney function at baseline		
Unadjusted	0.02 (-0.08; 0.11)	-0.03 (-0.37; 0.30)
Adjusted [b]	0.08 (-0.01; 0.17)	0.21 (-0.13; 0.55)

[a] 1 unit is 1 mL/min/1.73 m^2
[b]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* $P < 0.05$

Association of kidney function decline and symptom development

The trajectories of kidney function decline and development of both the number and severity of symptoms over time are presented in Figure 2. The mean (95%-CI) annual kidney function decline was 1.63 (1.26; 2.00) mL/min/1.73m^2. The mean (95%-CI) annual increase in number of symptoms was 0.73 (0.28; 1.19). Each unit (=1 mL/min/1.73m^2) annual decline of kidney function was associated with an adjusted extra annual increase in number of symptoms with 0.23 (0.07; 0.39) point (Table 4). Besides, the mean increase in overall symptom severity was 2.93 (1.34; 4.52) points per year. Thereby, the symptoms difficulty concentrating, restless legs and decreased appetite increased most severely over time. Each unit of annual kidney function decline was associated with an adjusted extra annual increase in overall symptom severity with 0.87 (0.35, 1.40) point (Table 4). In other words, a faster kidney function decline was associated with a steeper increase in both the number of symptoms and the overall severity of symptoms per year in patients with advanced CKD. These numbers correspond to 32% and 30% of the mean annual increase of 0.73 in symptom number and 2.93 in overall symptom severity, respectively. Figure 3 illustrates the impact of one additional unit decline of kidney function on the development of overall symptom severity in an average patient.

Table 4. Effect per unit decline in eGFR-MDRD (per year) on annual change in symptom number and severity

	Symptom number (N=1109)	Symptom severity (N=1019)
Mean annual increase (95%-CI)	0.73 (0.28; 1.19)*	2.93 (1.34; 4.52)*
Extra increase per unit[a] decline in kidney function		
Unadjusted	0.24 (0.08; 0.40)*	0.88 (0.34; 1.41)*
Adjusted [b]	0.23 (0.07; 0.39)*	0.87 (0.35; 1.40)*

[a] 1 unit is 1 mL/min/1.73 m^2 decline per year
[b] Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* $P < 0.05$

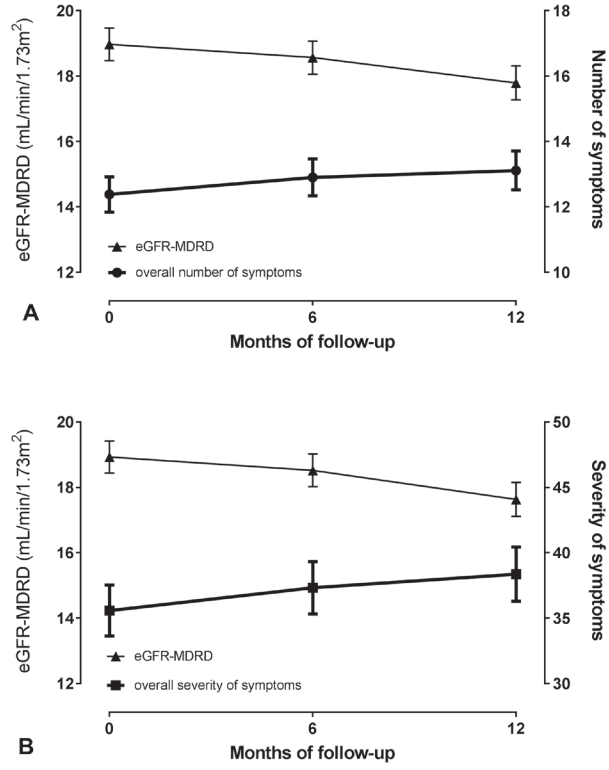

Figure 2. Overall mean (95% CI) trajectories, based on estimated marginal means, of kidney function decline and increase in number of symptoms (A) and mean (95% CI) kidney function decline and development of severity of symptoms over time in advanced CKD patients (B) .

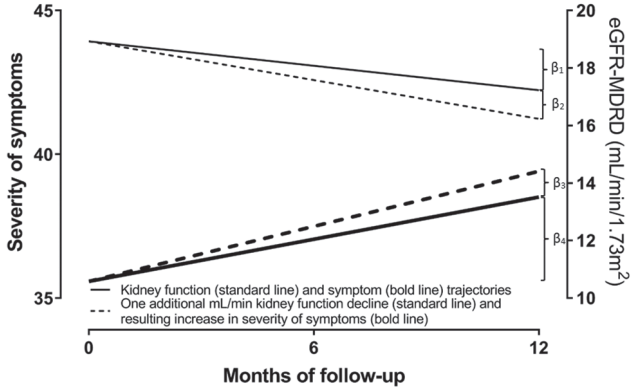

Figure 3. Illustration of the adjusted mean annual slopes of kidney function (β_1=1.70 mL/min/1.73m^2) and overall symptom severity (β_4=2.93) in a patient with average covariate values (solid line). Furthermore, we show the impact of one additional mL/min/1.73 m^2 kidney function decline (β_2=1.00 mL/min/1.73m^2) per year on the extra increase of the overall severity of symptoms over time (β_3=0.87). The additional kidney function decline and resulting increase in symptom severity is represented with the dashed lines, this results in a total decline of kidney function of $\beta_1+\beta_2$ (=2.70 mL/min/1.73m^2) and associates with a total increase in symptoms of $\beta_3+\beta_4$ (=3.80) per year.

Sensitivity analyses

Using the CKD-EPI instead of the MDRD equation yielded comparable results (Supplemental Tables S3-S5). After 6 and 12 months of follow-up, there was no cross-sectional association between the level of kidney function and either the number or severity of symptoms (Supplemental Table S6). Repeating the longitudinal analyses with linear regression on individual slopes instead of linear mixed effects models yielded comparable results (Supplemental Tables S7-8). Also, repeating the analyses in individuals with complete questionnaire data on 13 disease-related symptoms did not materially change the results. Each unit decrease in kidney function decline was significantly associated with a more progressive increase in both number and overall severity of symptoms (Supplemental Tables S9-11). The association between kidney function decline and increase in overall symptom burden was slightly weaker.

DISCUSSION

In our study of older adults with advanced stage CKD, we found that a faster kidney function decline was associated with a steeper increase in the symptom burden over time in patients with advanced CKD. For each unit (=mL/min/1.73m^2) annual decline of kidney function the increase in number and severity of symptoms steepens with 0.23 and 0.87 per year. This may seem modest, but is corresponding to approximately 30% of the mean annual increase in both

symptom number and severity. We found neither a cross-sectional association in level of kidney function and symptoms nor an association between baseline kidney function and symptom development during the pre-dialysis phase.

The symptom burden was substantial in our study population, which has been shown previously at baseline.[30] The symptom number at cohort entry is in concordance with observations in literature, reporting an average number of symptoms between 6 to 20 symptoms in patients with CKD.[6, 31] Our symptom severity was somewhat higher than reported by Almutary *et al.*[25] Our mean annual increase in number of symptoms was similar to the increase of approximately half a symptom found in the 24 to 12 months prior to reaching the endpoint dialysis, transplantation or death in the study of de Goeij *et al.*[9] We found a mean (95% CI) increase in symptom severity of 2.93 (1.34; 4.52) per year. Our study is the first study that examined the increase in symptom severity over time in CKD patients. It is important to distinguish between symptom number and symptom severity in each individual patient.[4, 25] A higher symptom number does not necessarily mean that these patients experience a higher symptom severity. In a previous EQUAL study, we demonstrated that both symptom number and symptom severity influence the patient reported health related quality of life.[2] The contribution of symptoms to the quality of life variable was also larger than any other condition (e.g. age, comorbidity) investigated.

The pathophysiological mechanisms underlying the onset of these symptoms and the interplay with kidney function are still not fully understood.[32] It is expected that with disease progression, the subjective manifestation of that condition (i.e. symptoms) will increase. This assumption also seems applicable to the symptom development in patients with advanced CKD: an increased number of symptoms and an increased symptom severity was experienced by patients with a faster kidney function decline. However, this relationship is not as straightforward as it appears. As in previous research that explored the relationship between kidney function and symptoms, we found no cross-sectional association between the level of kidney function and either symptom number or severity.[3, 9, 33, 34] Murphy *et al* found no cross-sectional association between eGFR and either symptom number or severity in conservatively managed patients with advanced CKD.[3] Furthermore, de Goeij *et al* showed that symptoms and eGFR-MDRD were not correlated in patients with CKD stage 4-5 at four different time points during pre-dialysis care.[9] Apparently, the symptom score varies widely in patients with the same kidney function, considering the absence of these associations, and several possible explanations exist for these differences. First, the timing of symptom onset differs between patients, i.e. at different levels of kidney function.[9, 29] Second, literature suggests that, in addition to disease progression

itself, social and psychological determinants play an important role in symptom development.[32] In particular psychological determinants are deemed to be relevant for patients' experience of symptoms and their perception of symptom burden, for example: illness perceptions and coping strategies.[32, 35, 36] Thus, the lack of cross-sectional associations could be because patients with the same kidney function could report a variety of symptom number and severity due to differences in psychological factors.[33-38] In addition, CKD patients often have several comorbid conditions that would also contribute to the overall symptom burden. All of the above would dilute the true effect of symptoms caused by low kidney function in any cross-sectional investigation. Studying the effect of kidney function loss and symptom development over time makes it easier to disentangle the association with kidney function on symptom burden *per se*.

To our knowledge, this is the first study that examined the longitudinal association between change in kidney function and change in symptoms over time in patients with advanced CKD. In contrast to our findings, Brown *et al* found no association between categories (stable, improved or worsening) of symptoms and stable or decline in eGFR in elderly non-dialysis patients with CKD stage 5.[39] However, we investigated the continuous change in kidney function and symptoms. The lack of an association in the study of Brown *et al* could be explained by the lack of adjustment for confounding and the loss of information by categorizing the change in symptoms. We extended these findings by showing the impact of a faster kidney function decline on the more progressive increase in symptoms over time in patients with advanced CKD, including adjustment for confounding. In addition, further research on this topic is warranted to unravel the mechanisms underlying the interplay between kidney function decline and symptom development, and the possible role of psychological factors (e.g. illness perceptions) in the onset and development of symptoms. It is important that healthcare professionals continue to focus on supporting patients in finding a way to deal with complaints and symptoms.[40]

A major strength is that the EQUAL study is a large European multicentre prospective cohort study of incident patients with advanced CKD of at least 65 years old. This allowed us to examine the longitudinal association between kidney function decline and symptom development. The study design with a combination of limited exclusion criteria and the elimination of survivor bias by following patients from a common starting point (defined as incident eGFR ≤ 20 mL/min/1.73 m^2), increases the generalizability of the obtained results to the clinical practice of pre-dialysis care for elderly patients. Limitations include the use of a single eGFR at each time point, possibly not reflecting the variability in eGFR. However, this is common in real-world clinical practice. Furthermore, the current analysis is restricted to the responders with at

least one follow-up measurement. However, baseline characteristics of these responders are similar to characteristics of excluded patients. Furthermore, comparable results were obtained when confining the analyses to the 13 CKD-related symptoms or individuals with three measurements available of kidney function and symptoms. We should note that the advanced age of the cohort limits the generalizability to the whole non-dialysis patient population with CKD stage 4-5 and results should only be generalized to patients of at least 65 years old. We should acknowledge the possible limitations of the use of eGFR estimated based on serum creatinine, since serum creatinine excretion declines in elderly and is determined by person's size and muscle mass. Furthermore, we assigned an equal weight to all symptoms to build a sum score based on the methodology of Abdel-Kader *et al.*[15] However, some symptoms could be more burdensome than others, although literature on this is scarce, therefore we were not able to assign different weights to each symptom. Finally, the DSI is the most commonly used symptom questionnaire, although developed and validated in dialysis patients. However, the DSI has been used in non-dialysis dependent patients before.[41, 42] The DSI is used in the EQUAL study, because the EQUAL study captures the pre-dialysis, transition, and dialysis phase.

Although healthcare providers are aware of the symptom burden in patients with advanced CKD, and evaluation of symptoms are rated as important in the KDIGO guidelines,[8] the evidence behind this recommendation is "not graded". This complicates anticipating treatment choices and advising when to initiate dialysis for symptom relief. Our results seem to suggest that repeated thorough assessment of both symptom burden and severity, in addition to the monitoring of kidney disease progression, is important throughout the pre-dialysis period, for instance using Patient Reported Outcomes Measures (PROMs). Current research such as the SWIFT (symptom monitoring with feedback trial) in Australia/New Zealand and OPT-ePRO (OPTimising routine collection of electronic Patient-Reported Outcomes into disease registries) in the UK are investigating the effectiveness of routinely capturing PROMs in renal care. The underlying purpose is to improve symptom control, to reduce symptom number and severity, and to prepare for end stage kidney disease care. Developing better treatments to reduce symptoms of CKD is also suggested as a main research priority by patients.[7] Future research should focus on which CKD related symptoms possibly increase the most with kidney function deterioration. Additionally, uraemic signs and symptoms were rated as the most important factor guiding the timing of dialysis initiation in an international survey.[43] The important role of physical symptoms in deciding when to start dialysis, was also seen in the IDEAL study.[11] Furthermore, each additional sign or symptom has been shown to be associated with a higher odds for earlier dialysis initiation (odds ratio of 1.16 [95%-CI 1.06;

1.28] per symptom) in nursing home residents.[44] For future research it would be interesting to investigate whether the increase in symptom burden is associated with time to dialysis initiation or hospitalization, a longer follow-up would be needed in order to provide enough events. Ultimately, a clinical decision rule, including kidney function decline and symptom development, may be useful to decide what the optimal timing is for dialysis initiation. Of course, we have to keep in mind that nonspecific symptoms could be related to other comorbid conditions or illnesses precipitating early dialysis initiation among some providers.

To conclude, we showed that a faster kidney function decline associates with a more progressive increase in both overall symptom number and severity in patients with advanced CKD. Considering the modest association, our results seem to suggest that repeated thorough assessment of symptom development during outpatient clinic visits, in addition to the monitoring of kidney function decline, is important for clinical decision making.

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SUPPLEMENTARY MATERIAL

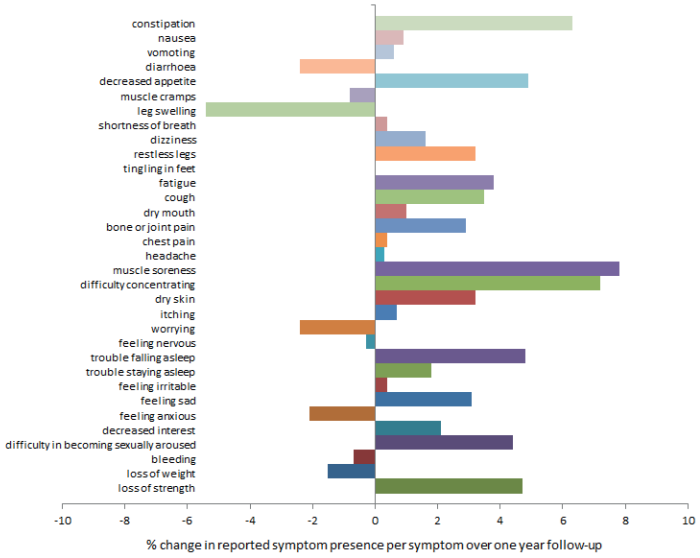


Figure S1. The percentage change in reported symptom presence for each symptom in our study population over the one year follow-up period.

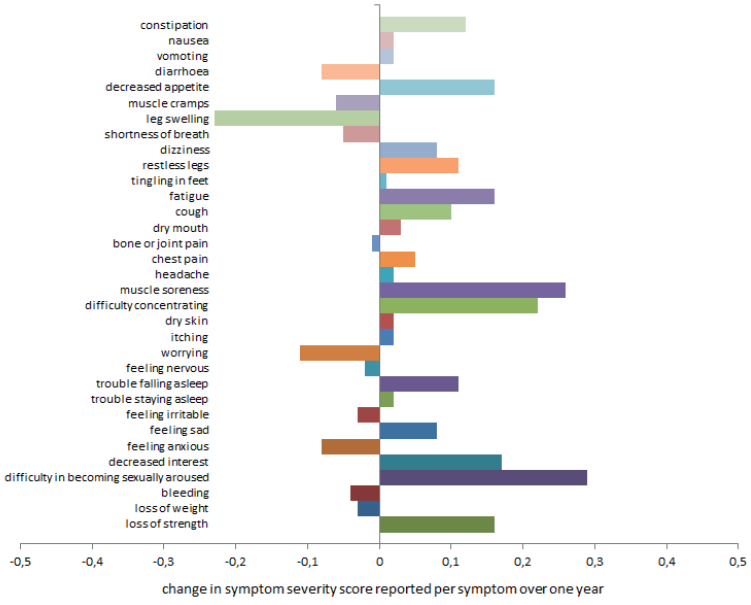


Figure S2. The change in symptom severity score reported for each symptom over the one year follow-up period. The symptom severity score reported for one symptom present, ranged between 1 to 5.

Table S1. Variable definitions

Variable(s)	Definition
Primary kidney disease	Primary kidney disease was classified by the treating nephrologist according to the codes of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA).[1] Patients were grouped into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases.
Educational level	Educational level was classified into low (no education or primary school only), intermediate (primary and secondary school) or high (academic) education.
Diabetes mellitus	Diabetes mellitus was defined as a composite of either type 1 or type 2 diabetes.
Psychiatric disease	Psychiatric disease was defined as the presence of a chronic mental disorder, mainly covering depression and dementia.
List of 33 symptoms	Constipation, nausea, vomiting, diarrhoea, decreased appetite, muscle cramps, leg swelling, shortness of breath, dizziness, restless legs, tingling in feet, fatigue, cough, dry mouth, bone or joint pain, chest pain, headache, muscle soreness, difficulty concentrating, dry skin, itching, worrying, feeling nervous, trouble falling asleep, trouble staying asleep, feeling irritable, feeling sad, feeling anxious, decreased interest in sex, difficulty in becoming sexually aroused, bleeding, loss of weight, loss of strength.
Uraemia- or disease-related symptoms	Nausea, decreased appetite, muscle cramps, restless legs, fatigue, itching, trouble falling asleep, trouble staying asleep, shortness of breath, bone or joint pain, loss of strength, difficulty concentrating and tingling in feet

[1] ERA/EDTA Registry. (ERA/EDTA) Registry Annual Report 2009. Amsterdam, The Netherlands: Academic Medical Center, Department of Medical Informatics; 2011.

Table S2. Baseline characteristics of excluded patients, i.e. without at least one observation with eGFR-MDRD and overall symptom score available during first year of pre-dialysis

	At least two visits with eGFR-MDRD and symptom number available at baseline, n=542 [a]	At least two visits with eGFR-MDRD and symptom severity available at baseline, n=632 [b]
Sex, male	313 (57.7)	379 (60.0)
Age, years	77.1 (71.3-82.7)	77.1 (71.6-82.5)
Ethnicity		
Caucasian	475 (91.9)	562 (92.7)
Black	17 (3.3)	17 (2.8)
Other	25 (4.8)	27 (4.5)
Primary Kidney Disease		
Glomerular disease	33 (6.1)	40 (6.3)
Tubulo-interstitial disease	35 (6.5)	41 (6.5)
Diabetes Mellitus	112 (20.7)	139 (22.0)
Hypertension	173 (31.9)	197 (31.2)
Other/ unknown	189 (34.9)	215 (34.0)
Education [c]		
No	3 (1.6)	6 (2.2)
Low	61 (31.8)	103 (37.3)
Intermediate	98 (51.0)	132 (47.8)
High	23 (12.0)	26 (9.4)
Other	7 (3.6)	9 (3.3)
Marital status, married or living together	102 (50.5)	154 (53.3)
Diabetes Mellitus, yes [d]	228 (44.8)	273 (45.7)
Hypertension, yes [e]	457 (91.0)	529 (90.4)
Cerebrovascular Disease, yes	78 (15.5)	94 (15.9)
Myocardial Infarction, yes	79 (15.5)	96 (16.1)
Malignancy, yes	106 (21.0)	124 (21.1)
Psychiatric disease, yes	24 (4.7)	35 (5.9)
Body Mass Index, kg/m²	28.9 (±5.4)	28.8 (±5.4)
eGFR baseline, ml/min/1.73m²	18.9 (±6.2)	19.1 (±6.2)
Serum albumin, g/L	38.0 (±5.9)	38.0 (±6.0)
Hemoglobin, mmol/L	7.2 (±0.9)	7.2 (±0.9)
Proteinuria, g/24h	1.4 (0.3-5.6)	1.4 (0.3-4.0)

Values are given as frequency (percentage), mean (±SD) or median (IQR), as appropriate.
[a] Missings: 4.6% ethnicity, 64.5% educational status, 62.7% marital status, 6.1% diabetes, 7.4% hypertension, 7.0% cerebrovascular disease, 6.1% myocardial infarction, 7.0% malignancy, 6.5% psychiatric disease, 15.3% BMI, 14.2% albumin, 5.5% hemoglobin, 68.3% proteinuria. [b] Missings: 4.1% ethnicity, 54.3% marital status, 56.3% educational status, 5.5% diabetes, 7.1% hypertension, 6.6% cerebrovascular disease, 5.5% myocardial infarction, 7.1% malignancy, 6.2% psychiatric disease, 13.8% BMI, 13.8% albumin, 5.2% hemoglobin, 68.6% proteinuria. [c] Defined as: low, no education or primary school only; intermediate, primary and secondary school; high, academic education. [d] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [e] Defined as either the presence of hypertension as primary kidney disease or a history of hypertension.

Main analyses repeated using CKD EPI-creatinine instead of MDRD formula

Table S3. Cross-sectional effect per unit lower eGFR CKD EPI-creatinine on symptom number and severity at baseline

	Symptom number (N=980)	Symptom severity (N=846)
Unadjusted	-0.001 (-0.08; 0.08)	-0.05 (-0.35; 0.25)
Adjusted [a]	0.01 (-0.07; 0.09)	0.09 (-0.20; 0.38)

[a]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at each specific time point (baseline, 6 or 12 months after cohort entry).

Table S4. Effect per unit lower eGFR CKD EPI-creatinine at baseline on annual change in symptom number and severity

	Symptom number (N=1104)	Symptom severity (N=1015)
Mean annual increase (95%-CI)	0.76 (0.30; 1.21)*	3.00 (1.41; 4.59)*
Extra increase per unit[a] lower kidney function at baseline		
Unadjusted	0.05 (-0.05; 0.14)	0.07 (-0.27; 0.42)
Adjusted [b]	0.08 (-0.01; 0.18)	0.22 (-0.13; 0.57)

[a] 1 unit is 1 mL/min/1.73 m^2
[b]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* P < 0.05

Table S5. Effect per unit decline in eGFR CKD EPI-creatinine (per year) on annual change in symptom number and severity

	Symptom number (N=1109)	Symptom severity (N=1019)
Mean annual increase (95%-CI)	0.73 (0.28; 1.19)*	2.93 (1.34; 4.52)*
Extra increase per unit[a] decline in kidney function		
Unadjusted	0.29 (0.09; 0.49)*	1.01 (0.38; 1.64)*
Adjusted [b]	0.26 (0.07; 0.45)*	0.96 (0.33; 1.59)*

[a] 1 unit is 1 mL/min/1.73 m^2 decline per year
[b]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* P < 0.05

Main analyses repeated using linear regression in individuals with 2 eGFR-MDRD estimates and either 2 symptom number or severity scores

Table S6. Cross-sectional effect per point decrease of eGFR-MDRD on change in symptom number and severity after 6 and 12 months of follow-up

	After 6 months	After 12 months
Number of patients	570	439
Symptom number, unadjusted	0.09 (-0.004; 0.18)	-0.02 (-0.11; 0.08)
Symptom number, adjusted [a]	0.09 (0.00; 0.18)	-0.03 (-0.13; 0.06)
Number of patients	506	398
Symptom severity, unadjusted	0.18 (-0.16; 0.52)	-0.12 (-0.46; 0.23)
Symptom severity, adjusted [a]	0.22 (-0.11; 0.56)	-0.11 (-0.46; 0.25)

[a]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at each specific time point (baseline, 6 or 12 months after cohort entry).

Table S7. Effect per point decrease of eGFR-MDRD at baseline on symptom number and severity over time

	Unadjusted	Adjusted [a]
Symptom number (n=632)	-0.13 (-0.34; 0.07)	-0.03 (-0.25; 0.18)
Symptom severity (n=572)	0.08 (-0.53; 0.69)	0.29 (-0.34; 0.93)

[a] Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.

Table S8. Overall change in symptoms and kidney function and the association between kidney function and symptom trajectories over time

	Mean increase (95% CI) in symptoms	Mean decline (95% CI) in eGFR
Population with at least 1 symptom number and eGFR-MDRD value (n=622)	0.38 (-0.72; 1.49)	1.70 (1.15; 2.25)*
Population with at least 1 symptom severity and eGFR-MDRD value (n=563)	3.13 (0.05; 6.22)*	1.90 (1.31; 2.48)*
Mean (95% CI) extra increase in symptom score per additional mL/min/1.73 m² decrease in kidney function decline per year		
	Unadjusted	Adjusted [a]
Symptom number	0.35 (0.19; 0.51)*	0.34 (0.19, 0.50)*
Symptom severity	0.92 (0.49; 1.35)*	0.85 (0.41, 1.30)*

[a]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* $P < 0.05$

Main analyses repeated for 13 CKD-related symptoms

Table S9. Cross-sectional effect per point decrease of eGFR-MDRD on change in symptom number and severity

	Cohort entry
Number of patients	1031
Symptom number, unadjusted	0.01 (-0.03; 0.04)
Symptom number, adjusted [a]	0.01 (-0.02; 0.04)
Number of patients	986
Symptom severity, unadjusted	0.01 (-0.11; 0.13)
Symptom severity, adjusted [a]	0.03 (-0.09; 0.15)

[a]Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at each specific time point (baseline, 6 or 12 months after cohort entry).

Table S10. Effect per point decrease of eGFR-MDRD at baseline on symptom number and severity over time

	Unadjusted	Adjusted [a]
Symptom number (n=1226)	0.01 (-0.03; 0.05)	0.04 (0.003;0.08)*
Symptom severity (n=1188)	-0.01 (-0.15; 0.13)	0.09 (-0.05; 0.23)

[a] Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.

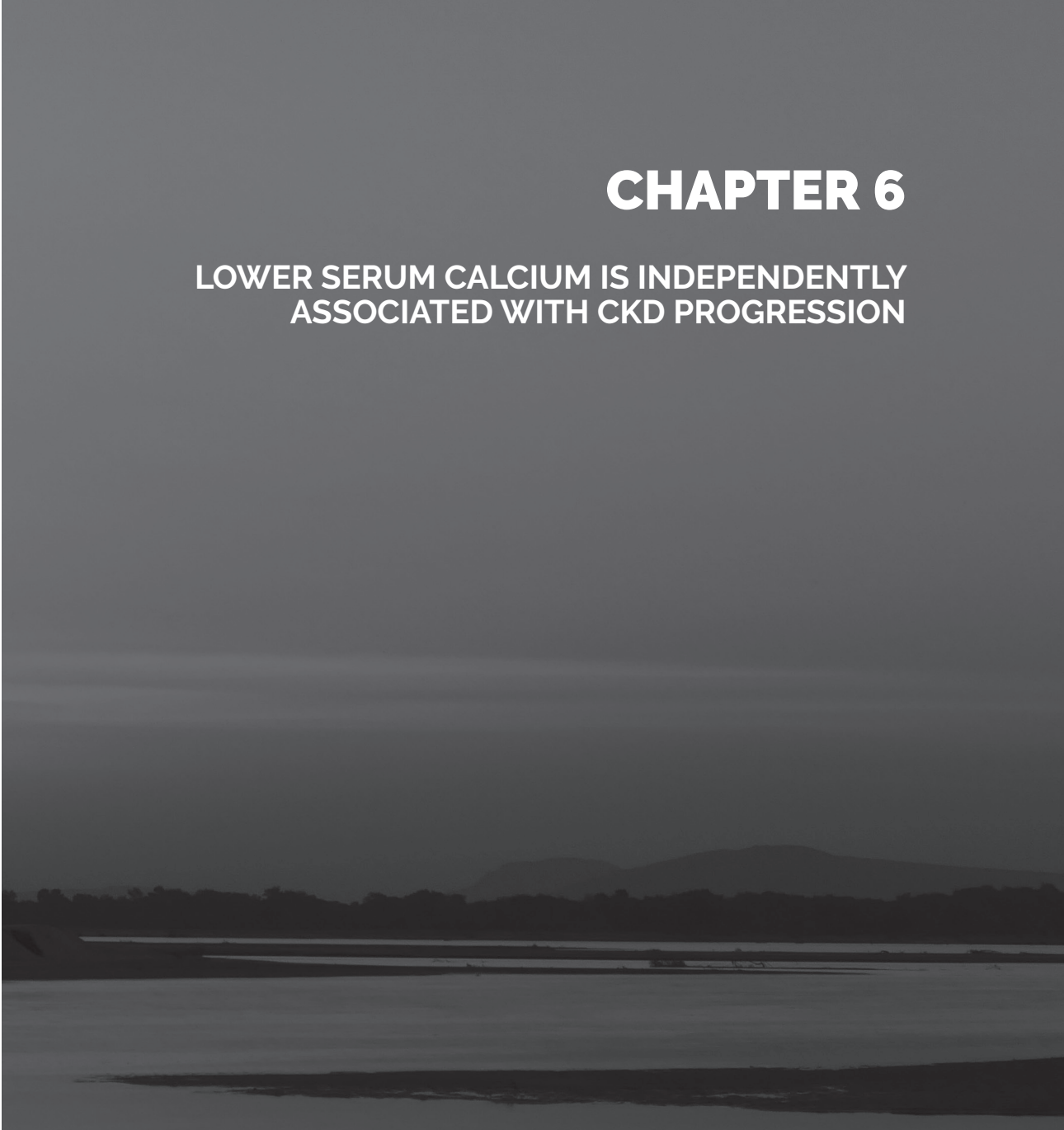
Table S11. Overall change in symptoms and kidney function and the association between kidney function and symptom trajectories over time

	Mean increase (95% CI) in symptoms	Mean decline (95% CI) in eGFR
Population with at least 1 symptom number and eGFR-MDRD value (n=1234)	0.36 (0.16; 0.56)*	1.56 (1.21; 1.92)*
Population with at least 1 symptom severity and eGFR-MDRD value (n=1196)	1.25 (0.57; 1.93)*	1.58 (1.21; 1.95)*
Mean (95% CI) extra increase in symptom score per additional mL/min/1.73 m² decrease in kidney function decline per year		
	Unadjusted	Adjusted [a]
Symptom number	0.14 (0.07; 0.21)*	0.14 (0.06; 0.21)*
Symptom severity	0.50 (0.25; 0.75)*	0.51 (0.26; 0.76)*

[a] Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, hemoglobin, proteinuria at baseline.
* $P < 0.05$

CHAPTER 6

LOWER SERUM CALCIUM IS INDEPENDENTLY ASSOCIATED WITH CKD PROGRESSION



Cynthia J. Janmaat, Merel van Diepen, Alessandro Gasparini, Marie Evans, Abdul Rashid Qureshi, Johan Ärnlöv, Peter Barany, Carl-Gustaf Elinder, Joris I. Rotmans, Marc Vervloet, Friedo W. Dekker, Juan Jesus Carrero

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ABSTRACT

Disturbances in calcium metabolism are common in individuals with chronic kidney disease (CKD), but whether they are associated with subsequent kidney function decline is less clear. In a CKD 3-5 cohort of 15,755 adult citizens of Stockholm with creatinine tests taken during 2006-2011 and concurrent calcium testing at cohort entry, we investigated the association between baseline serum calcium and the subsequent change in estimated glomerular filtration rate (eGFR, by CKD-EPI) decline using linear mixed models. Mean (SD) baseline corrected serum calcium was 9.6 (0.5) mg/dL. Mean (95%-confidence interval [CI]) eGFR decline was -0.82 (-0.90; -0.74) mL/min/1.73m^2/year. In advanced CKD stages, higher baseline serum calcium was associated with less rapid kidney function decline. The adjusted change (95%-CI) in eGFR decline associated with each mg/dL increase in baseline serum calcium was -0.10 (-0.28; 0.26), 0.39 (0.07; 0.71), 0.34 (-0.02; 0.70) and 0.68 (0.36; 1.00) mL/min/1.73m^2/year for individuals in CKD stage 3a, 3b, 4, and 5, respectively. In a subgroup of patients using vitamin D supplements, the association between baseline serum calcium and CKD progression was eliminated, especially in CKD stage 3b and 4. To conclude, in individuals with CKD stage 3b to 5, lower baseline corrected serum calcium, rather than higher baseline serum calcium, associated with a more rapid CKD progression. Lower serum corrected calcium seems to be indicative for vitamin D deficiency.

INTRODUCTION

The identification of modifiable risk factors for chronic kidney disease (CKD) progression is important to the design, study and implementation of preventive strategies.[1, 2] Disturbances in mineral metabolism are prevalent in advanced CKD stages and have been suggested not only to be the consequence of CKD, but also a potential cause for a more rapid kidney function decline. [3, 4] Hyperphosphatemia has been consistently associated with CKD progression,[5-7] as well as FGF-23 excess and the calcium-phosphorus product.[8, 9] Less evidence exists on the association between calcium disturbances and kidney function decline, with two recent studies reporting conflicting and counterintuitive associations: While Schwarz et al.[8] found no association between calcium and CKD progression in CKD stage 1-5 patients, Lim et al.[10] reported low serum calcium to be associated with a faster kidney function decline in a pooled cohort of CKD stage 3-4 patients. Intuitively, it would be expected that high serum calcium concentrations contribute to rapid kidney function deterioration, due to precipitation of calcium-phosphorus product in vessels causing vascular calcifications,[11] or to acute effects of hypercalcemia. Preceding studies used a composite outcome of progression (50% decline or eGFR slope > -5 mL/min/1.73m^2 plus initiation of renal replacement therapy [RRT]), and did not investigate the absolute change in kidney function for each CKD stage. Furthermore, the kidney has compensatory mechanisms to maintain calcium-phosphate balance until late CKD stages,[12, 13] and therefore serum calcium may solely appear as overt risk factor for progression in advanced CKD.[12] To clarify this issue, we here aimed to determine the plausible association between serum calcium and subsequent kidney function decline in non-dialysis patients with CKD stages 3-5 separately from a large regional-representative healthcare system.

METHODS

Study design, setting and study subjects

The Stockholm CREAtinine Measurements (SCREAM) project is a healthcare utilization cohort from the sole healthcare provider in the region of Stockholm, Sweden (Stockholm County Council), described elsewhere in more detail.[14, 15] SCREAM collected healthcare information on all Stockholm residents over the age of 18 years with a valid personal identification number and who had a measurement of serum creatinine undertaken in in- or outpatient care during 2006-2011. For these individuals, all standard laboratory tests performed during the period were retrieved; the dataset was then linked to regional and national administrative databases with complete information on demographic data, healthcare utilization, diagnoses, validated end

stage renal disease outcomes, vital status and pharmacy-dispensed medicines. The institutional review board for use of de-identified data at Karolinska Institutet, Stockholm, Sweden and the Swedish National Board of Welfare approved the study. Because data is de-identified, no informed consent is necessary according to Swedish ethical rules.

From this healthcare utilization database, we constructed a cohort study with participants having CKD stages 3-5. The index date was the date of the first eGFR test available per adult participant at study entry. We then selected all those participants with eGFR <60 mL/min/1.73m^2 after entry to construct a cohort of individuals classified as having CKD stages 3-5. Of those, we selected participants that had a concurrent measurement of serum calcium (defined as a serum calcium test taken at index date of up to 90 days before index date). For the purpose of this study (progression of CKD), we excluded individuals with prior renal replacement therapy, as ascertained by linkage with the Swedish Renal Registry. We then derived information on comorbid history, concomitant medication use and laboratory values from the other linked data sources. Because this is a real-world healthcare database, the availability of other laboratory tests at the time of index date depends on healthcare use and physicians' ordering of the test.

Biochemical assessments and study covariates

All blood and urine laboratory tests were performed as part of a healthcare encounter. Biochemical assessments were performed routinely by three different laboratories that provide services to the region (Aleris, Unilabs and Karolinska). Inter- as well as intra-laboratory variation is considered minimal, with the three laboratories being frequently audited for quality and harmonization by the national Government-funded organisation EQUALIS (www.equalis.se). We considered only laboratory tests performed in the outpatient setting as they reflect stable medical conditions. Serum creatinine measurements were standardized to isotope dilution mass spectrometry. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, taking into account age, sex and serum creatinine. Data on ethnicity were not available by law, but we expected the misclassification of eGFR to be minimal, given the vast majority of residents in the Stockholm region is Caucasian. We extracted information of any concomitant testing, if available, of serum calcium, serum intact parathyroid hormone (iPTH), serum phosphorus, serum hemoglobin (Hb), serum albumin and dipstick albuminuria. To maximize the inclusion of data, we considered laboratory tests performed at index date or the closest to index date and up to 90 days before. Serum calcium levels were corrected for serum albumin by the conventional Payne's formula: corrected calcium = measured calcium (mg/dL) + 0.8 x (4- serum albumin [g/dL]).[16]

Other study covariates were considered as follows: Age was defined as age at index date and analyzed continuously. Comorbid history was calculated from ICD-10 codes issued during 5 years prior to index date, with the exception of Diabetes Mellitus history, which was ascertained over the preceding 25 years because of its non-transient nature and long-term effects. Charlson Comorbidity index domains were used for identification of major diseases.[17] According to these domains, cardiovascular disease was defined as acute myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease; Diabetes mellitus was considered as the composite of diabetes with and without complications. Hypertension was defined by *a)* relevant ICD-10 codes (ICD-10 I10-I15) and *b)* pharmacy dispensation of antihypertensive medication (ATC codes for diuretics C03, RAAS inhibitors C09, C03DA, beta-blockers C07 and calcium channel blockers C08). Information on drug-dispensations comes from linkage with the Swedish Prescribed Drug Registry, collecting information on all prescription drugs dispensed at Swedish pharmacies. For the purpose of this study, repeated dispensations of calcium supplements (ATC code A12AA04, A12AA06, A12AA12, A12AX), phosphate binders (ATC code V03AE), active vitamin D analogues (ATC code A11CC04, A11CC03, H05BX02, H05BX03) and diuretics (ATC code C03) were extracted. Intake of medication at study inclusion considered any dispensation in the 3 months prior to the baseline measurement.

Study exposure

The study exposure was serum calcium. To test the hypothesis that the association between serum calcium and CKD progression depends on CKD stage, analyses were stratified according to CKD stages at baseline. CKD staging 3-5 was based on KDIGO criteria (i.e. stage 3 eGFR 30–59 mL/min/1.73 m^2, stage 4 eGFR 15–29 mL/min/1.73 m^2 and stage 5 eGFR < 15 mL/min/1.73 m^2).[2] CKD stage 3 was further subdivided in stage 3a (eGFR 45–59 mL/min/1.73 m^2) and stage 3b (i.e. eGFR 30–44 mL/min/1.73 m^2).[18, 19]

Study outcome

The study outcome was the change in annual eGFR decline counted from the baseline. The rate of decline was defined as the absolute change in eGFR per year. This was calculated from all available consecutive eGFR measurements as performed in healthcare. In this analysis, patients were censored if they emigrated from the region, initiated renal replacement therapy, died or reached end of the observation period, which was December 31, 2011, whichever came first. Information on vital status was obtained via linkage with the Swedish Population Registry, and information on emigration from the region was supplied by the Healthcare provider records cross-matched with the regional censoring office.

Statistical analyses

Categorical variables are presented as percentage of total; continuous variables are presented as mean values with standard deviation (SD) or median with interquartile range, depending on distribution. Baseline characteristics are presented for the total study population and stratified by CKD stage. P-values are two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS version 23.0.

Missing values were imputed with multiple imputation methods using a fully conditional specification with 10 repetitions.[20-22] Besides potential confounders, all available baseline variables and follow-up time were used for imputation. Follow-up time was logarithmically transformed; age and baseline eGFR values were square root transformed before entering in the imputation model. Estimates and standard deviations were calculated in each imputation set and pooled into one overall estimate and standard deviation according to Rubin's rules.[23, 24] Multiple imputation is the preferred method compared to complete case analysis in case of missing data.[20, 25-27] Complete case analysis will lead to biased estimates and loss of power. The preference for multiple imputation is independent of the proportion of missingness up to 90%.[26]

Linear mixed models (LMM) with random intercept and slope were used to estimate the change in the annual rate of kidney function decline associated with one unit (1 mg/dl) increase in baseline calcium. This model examines how serial eGFR measurements depended on baseline serum calcium. Results are expressed as regression coefficients and 95% CIs. Results are reported as the absolute change in annual rate of decline in kidney function that can be attributed to a unit increase in calcium at baseline. A negative change indicates a greater decline due to calcium increase; and a positive change indicates less decline.[28] Progressive multivariable analyses were used to adjust for potential baseline confounders. In a first model, we adjusted for age, sex, presence of DM, CVD, hypertension, serum albumin and hemoglobin. In a second model, we further adjusted for serum phosphate, active vitamin D therapy and calcium supplements. We did not adjust for iPTH in the primary analysis because iPTH lies in the causal pathway of the hypothesis hereby tested.[29] Instead, iPTH adjustment was considered in a sensitivity analysis (see below). We neither adjusted for phosphate binder use, since these frequently contain calcium, as such acting as calcium supplements.[30] LMM analyses were stratified by CKD stage. To investigate a potential dose-response relationship between baseline serum calcium and eGFR decline across baseline eGFR levels, we included an interaction term with baseline eGFR in the complete dataset combining all CKD stages. For increasing baseline eGFR (i.e. lower CKD stage), the coefficient for this interaction term estimates the additional

change in kidney function decline associated with a unit (i.e. mg/dL) increase in baseline serum calcium.

To validate the robustness of our findings, several additional sensitivity analyses were performed: Analyses were repeated 1) adjusting for baseline eGFR levels; 2) in the subgroup of patients using vitamin D supplementation; 3) after adjustment for imputed albuminuria and iPTH. The additional adjustment for albuminuria was performed, given that active vitamin D deficiency contributes to progressive kidney function decline via albuminuria[31]; 4) adjusting for diuretics (ATC code C03) and hypertension (ICD-10 I10-15), separately; 5) categorizing calcium by quintiles of distribution. This was done to assess the potential of non-linear trends in the association between calcium and CKD progression; 6) using uncorrected serum calcium as the exposure, because the precision of this corrected value to predict the "gold standard" free (ionized) calcium is limited and because albumin might be a determinant of the outcome of interest[32, 33]; 7) selecting only participants whose corrected serum calcium was within the normal reference range (i.e. 8.6-10.2 mg/dL); 8) selecting only participants with at least 3 eGFR tests available during follow up; 9) complete-case analysis (without multiple imputation); and 10) Finally we used Cox proportional-hazards regression analysis for the assessment of the association between baseline serum calcium levels and subsequent risk of either a sustained GFR decline of more than 30% or the risk of RRT. These were considered secondary outcomes, because dichotomization of the outcome leads to loss of information and power.

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files). The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

RESULTS

Baseline characteristics

Out of a total of 65,070 adult individuals with an eGFR at study entry that qualified as CKD 3-5, we included 15,755 for whom concurrent calcium was measured. See figure 1 for a flowchart of patient inclusion. These patients had a total of 63,468 consecutive eGFR assessments during observation. Median (IQR) age was 79.9 (70.2-85.8) years, and 39% were men. Median (IQR) eGFR was 48.1 (37.2-55.0) mL/min/1.73 m^2. A total of 9,286 patients had CKD stage 3a, 4,190 patients had CKD stage 3b, 1,784 patients had CKD stage 4 and 495 patients had CKD stage 5. Baseline characteristics are shown in Table 1. The majority of participants had baseline

corrected calcium levels within the normal reference range, i.e. 8.6-10.2 mg/dL (2.15-2.55 mmol/L).[34] Only 1.1% and 7.4% of participants had hypo- and hypercalcemia, respectively. In participants with hypocalcemia, 30% received vitamin D therapy, and only one person received active vitamin D therapy. Participants with CKD stage 5 were younger and more often men than the patients with CKD stages 3a to 4. Diabetes mellitus, hypertension, albuminuria and hyperphosphatemia were more prevalent in CKD stage 5 compared to other CKD stages. CKD stage 5 participants used phosphate binders more often than other CKD stages, and those with CKD stages 4-5 more often used active vitamin D analogues and diuretics compared to stage 3. Twelve variables were used as potential confounders and used to impute missing values. Ten of these variables were complete in all patients. Hemoglobin and phosphorus, had 15% and 71% of missings, respectively. As anticipated from a healthcare extraction, a few participants had a dipstick albuminuria or an iPTH test taken at the index date. Because these variables were available for 13% and 8% of the total study population, respectively, they were not considered for multivariable adjustment in our primary analysis.

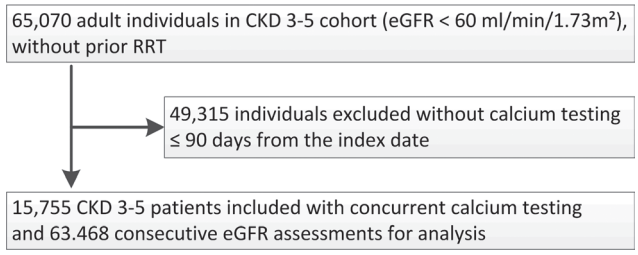

Figure 1. Flowchart of patient inclusion.

Table 1. Baseline characteristics of the study population by CKD stagea

	All (*n*=15755)	CKD 3a (*n*=9286)	CKD 3b (*n*=4190)	CKD 4 (*n*=1784)	CKD 5 (*n*=495)
Age (years)	79.9 (70.2-85.8)	79.0 (69.8-85.1)	81.9 (73.5-87.2)	80.1 (68.2-86.4)	73.2 (61.6-82.4)
Sex (% men)	6140 (39.0)	3323 (35.8)	1676 (40.0)	841 (47.1)	300 (60.6)
Comorbidities (%)[b]					
Diabetes mellitus	2352 (14.9)	1012 (10.9)	723 (17.3)	480 (26.9)	137 (27.7)
Cardiovascular disease	1502 (9.5)	722 (7.8)	479 (11.4)	251 (14.1)	50 (10.1)
Hypertension	9794 (62.2)	5035 (54.4)	2981 (71.1)	1411 (79.1)	399 (80.6)
Corrected calcium (mg/dl)*	9.5 ±0.5	9.5 ±0.5	9.6 ±0.5	9.5 ±0.6	9.6 ±0.9
Hypercalcemia (> 10.2 mg/dl)	1165 (7.4)	560 (6.0)	371 (8.9)	161 (9.0)	73 (14.7)
Hypocalcemia (< 8.6 mg/dl)	179 (1.1)	63 (0.7)	34 (0.8)	46 (2.6)	36 (7.3)
Vitamin D use (%)[c]	*55 (30.7)*	*4 (6.3)*	*6 (17.6)*	*19 (41.3)*	26 (72.2)
Active vitamin D use (%)[c]	*1 (0.6)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	1 (2.8)
Albumin corrected calcium (mg/dl)*	9.6 ±0.5	9.6 ±0.5	9.6 ±0.5	9.6 ±0.6	9.7 ±0.8
Serum albumin (g/l)*	37.0 ±4.1	37.5 ±3.8	36.6 ±4.1	35.8 ±4.5	35.4 ±4.8
Albuminuria (% yes)[c]	720 (4.6)	270 (2.9)	205 (4.9)	167 (9.4)	78 (15.8)
Baseline eGFR (ml/min/1.73 m²)	48.1 (37.2-55.0)	53.9 (49.9-57.2)	38.8 (34.9-42.2)	24.4 (20.3-27.5)	11.0 (8.5-13.1)
Number of repeated eGFR tests	5.0 (2.0- 13.0)	4.0 (1.0-10.0)	6.0 (2.0-13.0)	9.0 (4.0-17.0)	8.0 (4.0-15.8)
Phosphorus (mg/dl)	3.7 ±0.9	3.4 ±0.6	3.5 ±0.7	3.9 ±0.8	5.1 ±1.3
iPTH (pg/ml)*	143.8 ±144.6	72.8 ±49.1	104.0 ±67.5	161.1 ±125.5	270.2 ±249.5
Serum Hb (g/l)	131.5 ±16.0	134.7 ±15.2	129.2 ±15.7	123.8 ±15.7	119.1 ±16.5
Medication (%)					
Calcium supplements	105 (0.7)	88 (0.9)	15 (0.4)	1 (0.1)	1 (0.2)
Bisphosphonates	836 (5.3)	537 (5.8)	240 (5.7)	51 (2.9)	8 (1.6)
Phosphate binders	313 (2.0)	9 (0.1)	40 (1.0)	112 (6.3)	152 (30.7)
Vitamin D therapy	915 (5.8)	99 (1.1)	175 (4.3)	366 (20.5)	275 (55.6)
Active vitamin D use	*54 (0.3)*	*10 (0.1)*	*16 (0.4)*	*18 (1.0)*	10 (2.0)
Diuretics	7876 (50.0)	3842 (41.4)	2440 (58.2)	1252 (70.2)	342 (69.1)
Thiazide diuretics	*492 (3.1)*	*335 (3.6)*	*124 (3.0)*	*31 (1.7)*	*2 (0.4)*
Loop diuretics	*2184 (13.9)*	*995 (10.7)*	*689 (16.4)*	*410 (23.0)*	*90 (18.2)*

[a] Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as number (percentage).
[b] Comorbidities are deduced from Charlson domains.[c] These numbers only apply to patients with hypocalcemia (< 8.6 mg/dL).
[c] % Albuminuria is presented as percentage of the total study population, instead of the percentage of the patient population in which an actual albuminuria test was performed. Due to the missingness, the percentages shown are an underestimation of the actual percentage of albuminuria in the study population.
*To convert serum albumin in g/dl to g/l, multiply by 10; serum calcium in mg/dl to mmol/l, multiply by 0.2495; serum phosphorus in mg/dl to mmol/l, multiply by 0.3229; serum iPTH in pg/ml to ng/l, multiply by 1.

Association between baseline serum calcium and subsequent kidney function decline

The median (IQR) length of follow-up was 4.3 (2.0–5.3) years, and the median (IQR) number of eGFR measurements per patient was 5.0 (2.0-13.0). The overall mean annual rate of decline in patients with CKD stages 3a-5 was -0.82 (95% CI -0.903; -0.738) mL/min/1.73m^2, and the mean annual rate of decline was -0.657 (95% CI -0.775; -0.539), -1.013 (95% CI -1.175; -0.851), -1.457 (95% CI -1.634; -1.279) and -0.965 (95% CI -1.294; -0.636) mL/min/1.73m^2 for patients with CKD stage 3a, 3b, 4 and 5, respectively. The (adjusted) change in the rate of decline in kidney function associated with one unit higher (i.e. mg/dl) of serum calcium is shown in Table 2. While no association was observed between serum calcium at baseline and subsequent eGFR decline in patients with CKD stage 3a, a consistent negative association was found in the remaining CKD stages: in other words, for every unit higher in baseline serum calcium, the associated eGFR decline was slower. The other way around, lower baseline serum calcium is associated with a faster subsequent kidney function decline. The adjusted associations in these stages are substantial, ranging from an increase of 24% to 70% of the mean annual decline rate for every unit lower in serum calcium. Aforementioned is illustrated in figure 2, which shows the modelled longitudinal trajectories in eGFR associated with corrected baseline serum calcium levels in CKD stage 3a to 5. Provided in the figure are the calcium eGFR trajectories based on the fully adjusted linear mixed model for the mean corrected baseline calcium level per CKD stage, the lower (8.6 mg/dL) and upper (10.2 mg/dL) reference limits, assuming the mean and the mode from the study population in each CKD stage for continuous and categorical covariates, respectively. Furthermore, a dose-response relationship seemed present: for higher CKD stages, lower serum calcium was associated with a more rapid kidney function decline, i.e. the lower the eGFR, the stronger the effect of lower calcium on subsequent decline (Table 2). This was confirmed by multiplicative interaction tests between baseline eGFR and serum calcium (Table 3). The negative interaction term indicates a smaller coefficient for higher eGFR. Let us suppose the adjusted value of 0.019 mL/min/1.73m^2: This means given that we have one unit increase in baseline eGFR, one unit increase in baseline calcium results in a smaller additional change in eGFR decline of 0.019 mL/min/1.73m^2. In other words, the effect of serum calcium on kidney function decline is stronger, for lower baseline eGFR, thus the higher the CKD stage.

Table 2. Association between baseline corrected serum calcium and the subsequent rate of kidney function decline (95%-CI)

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per each mg/dL higher albumin-corrected calcium (negative = extra decline)[a]								
Raw data	-0.098 (-0.362; 0.165)	0.46	0.515 (0.196; 0.835)	0.002	0.428 (0.085; 0.772)	0.01	0.649 (0.323; 0.975)	<0.001
Model 1	-0.003 (-0.044; 0.038)	0.98	0.390 (0.073; 0.707)	0.02	0.328 (-0.003; 0.686)	0.07	0.683 (0.359; 1.008)	<0.001
Model 2	-0.009 (-0.277; 0.260)	0.95	0.391 (0.074; 0.708)	0.02	0.344 (-0.015; 0.704)	0.06	0.682 (0.355; 1.009)	<0.001

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Table 3. Multiplicative interaction tests between baseline corrected serum calcium and baseline eGFR in its association with subsequent kidney function decline (95%-CI)

	All patients (n=15755)	P*
Additional change in eGFR decline per each mg/dL higher albumin-corrected calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Raw data	-0.021 (-0.032; -0.009)	<0.001
Model 1	-0.019 (-0.030; -0.008)	0.001
Model 2	-0.019 (-0.030; -0.008)	0.001

Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

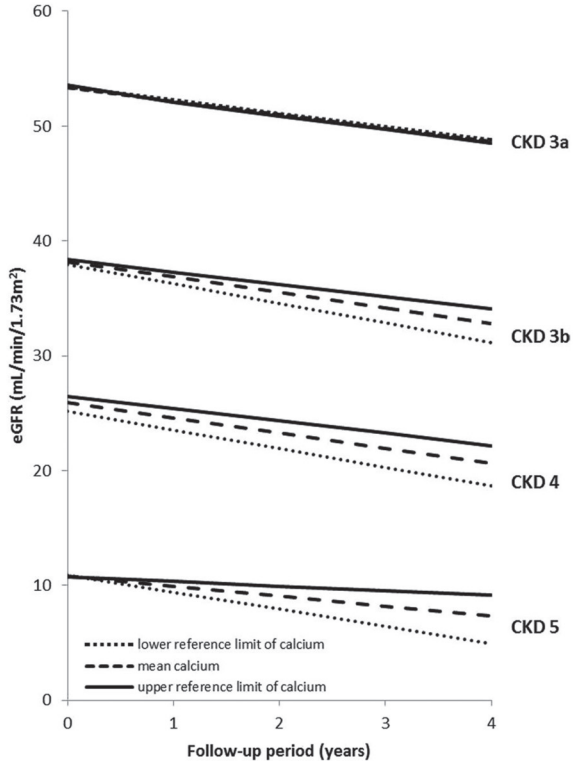

Figure 2. Modelled longitudinal trajectories in eGFR associated with corrected baseline serum calcium levels in CKD stage 3a, 3b, 4, and 5. Provided are the calcium GFR trajectories based on the fully adjusted linear mixed model for the overall mean corrected baseline calcium level, the lower (8.6 mg/dL) and upper (10.2 mg/dL) reference limits, assuming the mean for continuous covariates and the mode (most frequent values) for categorical covariates the study population in each CKD stage.

Sensitivity analyses

Various sensitivity analyses were performed; 1) Additional adjustment for baseline eGFR values yielded similar results (Supplementary Table S1 online). 2) A subgroup analysis in patients with vitamin D supplementation at baseline showed that the association between baseline corrected serum calcium and subsequent kidney disease progression is abrogated among users of vitamin D medication (Supplementary Table S2 online). 3) To test the possible impact of albuminuria and iPTH adjustment, we performed multiple imputation analysis on these covariates and observed comparable results in our models (Supplementary Tables S3a-b online). 4) Repeating the main analyses with separate adjustment for diuretics and hypertension yielded similar results (Supplementary Table S4 online). 5) Trend analysis in each CKD stage by quintiles of serum calcium distribution, suggested a gradual (and not a non-linear) higher rate of eGFR decline with lower serum calcium at baseline, in particular for patients with CKD stage 5 (Supplementary Table S5 online). 6) The magnitude of the association was confirmed when using uncorrected serum calcium (Supplementary Tables S6a-b online). 7) Similar results were obtained when repeating the analysis in patients with serum corrected calcium levels within the normal reference range (Supplementary Tables S7a-b online). 8) The results were similar when selecting individuals with at least 3 eGFR tests available (Supplementary Tables S8a-b online). 9) We observed similar associations in the complete case analysis (without imputation) (Supplementary Tables S9a-b online). 10) Finally, we tested the association between calcium and time to event analysis for dichotomous endpoints of CKD decline. In total, 629 (4%) patients started RRT, 1594 (10%) had a sustained GFR decline of more than 30% and 5436 (35%) died during follow-up. In the adjusted Cox proportional-hazards regression analysis, a borderline not significant lower risk of a sustained GFR decline of > 30% was present for each mg/dL increase in baseline corrected calcium levels, for both CKD stage 4 and 5. This association was not present in CKD stage 3a and 3b (Supplementary Table S10 online). In addition, adjusted Cox proportional-hazards regression analysis showed a trend towards higher risk of RRT with lower calcium levels at baseline (Supplementary Table S11 online). Although, this association was only significant for CKD stage 4, the observed trend is consistent with findings obtained from linear mixed models.

DISCUSSION

Intuitively, a higher serum calcium would be expected to be associated with a more rapid kidney function deterioration.[11] In contrast, we demonstrate in this study that lower baseline serum calcium, already within the normal reference range, is associated with a subsequent more rapid eGFR decline in individuals with CKD stages 3b-5. We showed that the adjusted change in kidney function decline was attenuated by a value between 0.34 and 0.68 mL/min/1.73m^2 for CKD stages 3b to 5, which corresponds to 24 -70% reduction of the mean annual decline rate, for every unit increase in calcium. Thus, the effects are potentially large; especially considering that serum calcium can easily vary between 9 and 10 mg/dL in these patients. This observation confirms and expands previous literature and underscores the need for a better understanding of the role of calcium in CKD progression.[8, 10] Strengths of our analysis are its large, real-world healthcare setting, the study of kidney function decline rate, and the *a priori* separation of CKD stages, allowing weighing the relative contribution of calcium to CKD progression rate for each CKD stage.[12, 13]

Our observational study does not allow inference of causality in the association between serum calcium and CKD progression. Our results are similar to those of Taylor et al., who showed that a low, rather than high, urinary calcium excretion associated with increased risk of CKD.[35] Current knowledge of the pathophysiology of CKD-MBD favors the argument of lower calcium being a risk marker and/or proxy of other underlying processes: In the natural history of (untreated) CKD progression, hypocalcemia usually develops and is associated with secondary hyperparathyroidism.[36] Physiologically, 1,25-dihydroxyvitamin D3 (1,25$(OH)_2$D3) enhances intestinal calcium absorption. Since declining of 25(OH)D3 and especially 1,25$(OH)_2$D3 is an early feature of CKD, hypocalcemia in CKD is generally considered to be a consequence of that.[12] Low levels of the 25(OH)D3 substrate may contribute to decreased levels of 1,25$(OH)_2$D3 production, particularly in CKD patients with nephrotic range proteinuria.[12] Therefore, it is possible that a lower serum calcium in this setting might indicate suboptimal supplementation of vitamin D deficiency, assuming a pathophysiological role in CKD progression of vitamin D deficiency. Both experimental and epidemiologic studies have shown that 25(OH)D3 deficiency itself might contribute to a progressive decline in kidney function.[37-39] In a subgroup analysis in patients using vitamin D supplements at baseline, we observed that the association between baseline serum calcium and subsequent kidney disease progression was abbrogated in participants with CKD stage 3b and 4, which supports the hypothesis that a lower serum corrected calcium at baseline may be indicative for vitamin D deficiency. Also, in CKD stage 5 the association between lower serum calcium concentrations and CKD progression was

attenuated among vitamin D users, although not abbrogated. This might indicate suboptimal supplementation of native vitamin D in this patient group, which indeed in general has the highest dose requirements. In addition to the role of 25(OH)D3, the impaired kidney function in CKD patients results in limited capacity to produce $1,25(OH)_2D3$ out of 25(OH)D3, due to the smaller amount of 1α-hydroxylase. Because of the low prevalence of active vitamin D use in our study population (sampled shortly before this medication entered in the Swedish market), correcting for active vitamin D therapy did not influence our results and the results should be interpreted with caution. Recently, low $1,25(OH)_2D3$ levels has been attributed to FGF23 accumulation.[40, 41] In turn, elevated levels of FGF-23 have been consistently associated with CKD progression[42, 43] and could in itself be a risk factor for kidney function decline via increased phosphate excretion per nephron, not mediated by $1,25(OH)_2D3$.[9, 44] Furthermore, Jean et al. showed that the use of oral cholecalciferol corrected vitamin D deficiency in dialysis patients, thereby also increasing the level of serum $1,25(OH)_2D3$ threefold.[45] Altogether, we speculate that mainly decreased vitamin D concentrations and associated suboptimal native vitamin D supplementation, and/or elevated FGF23, explain the association between lower serum calcium and CKD progression observed in CKD stages 3b to 5. This remains an observational study and in any case, the finding that lower serum calcium increases the rate of kidney function decline needs confirmation and further exploration in experimental studies.

Various limitations of this study should be considered. We found a low annual eGFR decline of 0.82 mL/min/1.73m^2, which may seem low but it is however similar to what is reported in other healthcare utilization cohorts.[46] Furthermore, this is a CKD 3-5 cohort derived from a healthcare utilization database, and the indications for calcium and creatinine testing rendered a population selection of mainly elderly individuals. This old age may also be partially responsible for the overall low mean annual eGFR decline.[47, 48] We also found a mortality rate of 35%, exceeding the total number of events of RRT (10%). However, it is broadly accepted that rates of death exceed those of RRT, especially in older age groups. This has been previously described in other healthcare cohorts.[46, 49]Moreover, the association between serum calcium at baseline and subsequent annual eGFR decline was assumed to be linear and this is hard to confirm definitively. However, we performed trend analyses and showed that a linear assumption for the studied association seems justifiable. Another limitation is that our real-world healthcare utilization nature limits our capacity to have a full set of covariates (they are available only if the physician ordered the test), and we used multiple imputation to test as a sensitivity analysis the impact of correcting for iPTH and dipstick albuminuria. Multiple imputation is a preferred method independent of the proportion of missingness, if two assumptions are met: the number of observations should be sufficient and missing data should be reasonably related to observed

patient characteristics (missing at random or MAR).[26] We believe that both assumptions are easily met in our study. Further, it is uncertain if albuminuria can be regarded a confounder or, instead, to be within the causal pathway, and that is why we regard this as sensitivity analysis. A final limitation is that we did not have laboratory information on urine albumin/creatinine ratio, FGF23 levels, ionized calcium, 25(OH)D3 levels or HbA1c levels. Considering the above, the uncertainty of the results should be kept in mind.

The recently updated KDIGO guidelines on CKD-MBD management emphasize the need for optimal monitoring of serum calcium in CKD stages 3-5, based on the presence and magnitude of abnormalities.[50, 51] In addition, guidelines suggest avoiding hypercalcemia, and state that mild and asymptomatic hypocalcemia can be tolerated in order to avoid inappropriate calcium loading. Furthermore, rising PTH levels or above the upper limit should be evaluated for hypocalcemia or vitamin D deficiency. However, solid evidence what the appropriate level is for lower serum calcium is lacking. We propose that low calcium levels may be interpreted as a proxy for increased FGF23 or deficiency of vitamin D in clinical practice. If the lower serum calcium levels are indeed indicative for either vitamin D deficiency or FGF23 excess, interventions should aim to restore this disorder. Possible interventions should not involve calcium supplementation, but most likely instead the prescription of native vitamin D, as also advised in current KDIGO guidelines, especially when a deficiency is established or suspected based on calcium levels.[32,33] In order to investigate the causal role of serum calcium in CKD progression, a RCT with vitamin D therapy would be required. The use of calcium supplements in CKD patients raises concerns about safety, given the attention to the plausible risks of calcium overload.[52, 53] However, partly because of this, the potential role of lower serum calcium in CKD progression may not be recognized.

In summary, we showed in our large CKD 3-5 cohort that lower serum calcium, already within the normal reference range, was associated with a subsequent faster kidney function decline in individuals with CKD stages 3b, 4 and 5 not requiring dialysis. This association remained after adjustment for various confounders. Lower serum calcium may be indicative for vitamin D deficiency. If confirmed, these results may have clinical implications for disease-preventive strategies and emphasize the need to better delineate the role of calcium in the course of disease.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Association between baseline corrected serum calcium with the subsequent rate of kidney function decline (95% CI) – additional adjustment for baseline eGFR

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per mg/dL increase in for albumin corrected calcium at baseline (negative = greater decline; positive = less decline)[a]								
Model 3	-0.027 (-0.488; 0.542)	0.92	0.353 (0.034; 0.671)	0.03	0.295(-0.062;0.653)	0.11	0.704 (0.363; 1.044)	<0.001

[a] In mL/min/1.73 m^2 per year
Model 3 adjusted for covariates in model 2 plus eGFR values at baseline
*P-value for difference in the change in the rate of kidney function decline with one unit increase in calcium

Supplementary Table S2. Association between baseline corrected serum calcium and the subsequent rate of kidney function decline (95%-CI) in the subgroup of patients with vitamin D supplementation at baseline

	CKD 3b (*n*=175)	P*	CKD 4 (*n*=366)	P*	CKD 5 (*n*=275)	P*
Change in eGFR decline per each mg/dL higher albumin-corrected calcium (negative = extra decline)[a]						
Raw data	-0.366 (-1.290; 0.559)	0.44	0.436 (-0.127; 0.999)	0.13	0.678 (0.311; 1.046)	<0.001
Model 1	0.310 (-1.280; 0.661)	0.53	0.371 (-0.217; 0.959)	0.22	0.469 (0.068; 0.869)	0.02
Model 2	-0.309 (-1.286; 0.667)	0.54	0.375 (-0.215; 0.965)	0.21	0.446 (0.039; 0.853)	0.03
Model 3	-0.283 (-1.265; 0.700)	0.57	0.365 (-0.227; 0.956)	0.23	0.403 (-0.003; 0.810)	0.05

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus and calcium supplements
Model 3 adjusted for covariates in model 2 plus active vitamin D therapy
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S3a. Association between baseline corrected serum calcium with the subsequent rate of kidney function decline (95% CI) – additional adjustment for both albuminuria and iPTH at baseline

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per mg/dL increase in for albumin corrected calcium at baseline (negative = greater decline; positive = less decline)[a]								
Model 3	-0.009 (-0.278; 0.260)	0.95	0.392 (0.075; 0.710)	0.02	0.343 (-0.017; 0.703)	0.06	0.683 (0.357; 1.008)	<0.001

[a] In mL/min/1.73 m^2 per year
Model 3 adjusted for covariates in model 2 plus albuminuria and iPTH at baseline
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S3b. Multiplicative interaction tests between baseline corrected serum calcium and baseline eGFR in association with kidney function decline 95% CI) – additional adjustment for both albuminuria and iPTH at baseline

	All patients (n=15755)	P*
Additional change in eGFR decline per each mg/dL higher albumin-corrected calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Model 3	-0.019 (-0.030; 0.008)	0.001

Model 3 adjusted for covariates in model 2 plus albuminuria and iPTH at baseline
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S4. Association between baseline corrected serum calcium with the subsequent rate of kidney function decline (95% CI) – model 1 of the main analysis adjusted for hypertension and diuretics, separately

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per mg/dL increase in for albumin corrected calcium at baseline (negative = greater decline; positive = less decline)[a]								
Model 1a	-0.032 (-0.288; 0.222)	0.81	0.384 (0.066; 0.702)	0.02	0.355 (-0.002; 0.711)	0.05	0.675 (0.350; 0.999)	<0.001
Model 1b	-0.014 (-0.217; 0.189)	0.92	0.387 (0.070; 0.704)	0.02	0.353 (-0.003; 0.710)	0.05	0.674 (0.351; 0.998)	<0.001

[a] In mL/min/1.73 m^2 per year
Model 1a adjusted for age, sex, DM, CVD, serum albumin, hemoglobin and blood pressure (defined as presence hypertension
Model 1b adjusted for age, sex, DM, CVD, serum albumin, hemoglobin and diuretics
*P-value for difference in the change in the rate of kidney function decline with one unit increase in calcium

Supplementary Table S5. Association between quintiles of baseline corrected serum calcium and subsequent rate of decline in kidney function (95% CI)

	CKD 3a (n=9286)	P*	CKD 3b (n=4190)	P*	CKD 4 (n=1784)	P*	CKD 5 (n=495)	P*
Change in eGFR decline per mg/dL increase in albumin corrected calcium at baseline (negative = greater decline; positive = less decline)[a]								
Raw data								
Q1 (<9.2)	0.153 (-0.245; 0.552)	0.45	-0.605 (-1.121; -0.899)	0.02	-0.857 (-1.419; -0.296)	0.003	-0.960 (-1.837; -0.082)	0.03
Q2 (9.2-9.4)	0.087 (-0.311; 0.485)	0.67	-0.702 (-1.217; -0.187)	0.01	-0.490 (-1.419; 0.230)	0.11	-0.862 (-1.927; 0.203)	0.11
Q3 (9.4-9.6)	-0.094 (-0.489; 0.299)	0.64	-0.660 (-1.164; -0.157)	0.01	-0.826 (-1.392; -0.261)	0.004	-0.729 (-1.832; 0.373)	0.20
Q4 (9.6-9.9)	-0.116 (-0.509; 0.277)	0.56	-0.447 (-0.949; 0.055)	0.08	-0.531 (-1.111; 0.049)	0.07	-0.272 (-1.227; 0.683)	0.58
Q5 (>9.9)	reference		reference		reference		reference	
Model 1								
Q1 (<9.2)	0.047 (-0.340; 0.434)	0.82	-0.336 (-0.853; 0.181)	0.20	-0.740 (-1.328; -0.153)	0.01	-0.985 (-1.888; -0.083)	0.03
Q2 (9.2-9.4)	-0.011 (-0.409; 0.388)	0.96	-0.569 (-1.076; -0.061)	0.03	-0.393 (-0.997; 0.209)	0.20	-0.877 (-1.957; 0.204)	0.11
Q3 (9.4-9.6)	-0.181 (-0.570; 0.207)	0.37	-0.559 (-1.052; -0.066)	0.03	-0.729 (-1.301; -0.156)	0.01	-0.587 (-1.687; 0.512)	0.29
Q4 (9.6-9.9)	-0.205 (-0.594; 0.184)	0.30	-0.345 (-0.835; 0.145)	0.17	-0.506 (-1.086; 0.075)	0.09	-0.104 (-1.053; 0.845)	0.83
Q5 (>9.9)	reference		reference		reference		reference	
Model 2								
Q1 (<9.2)	0.060 (-0.345; 0.464)	0.77	-0.340 (-0.856; 0.176)	0.20	-0.749 (-1.337; -0.161)	0.01	-0.953 (-1.876; 0.031)	0.04
Q2 (9.2-9.4)	-0.004 (-0.403;0.395)	0.99	-0.567 (-1.072; 0.059)	0.03	-0.383 (-0.989; 0.221)	0.21	-0.869 (-1.963; 0.225)	0.12
Q3 (9.4-9.6)	-0.171 (-0.562;0.221)	0.39	-0.564 (-1.056; 0.072)	0.03	-0.722 (-1.296; -0.148)	0.01	-0.584 (-1.707; 0.538)	0.31
Q4 (9.6-9.9)	-0.200 (-0.589;0.189)	0.31	-0.356 (-0.846; 0.134)	0.15	-0.504 (-1.088; 0.081)	0.09	-0.103 (-1.063; 0.858)	0.83
Q5 (>9.9)	reference		reference		reference		reference	

[a] In mL/min/1.73 m^2 per year
Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit increase in calcium

Supplementary Table S6a. Association between baseline serum calcium (not albumin-corrected) with subsequent rate of decline in kidney function (95% CI)

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per mg/dL increase in calcium at baseline (negative = greater decline; positive = less decline)[a]								
Raw data	0.299 (0.053; 0.544)	0.02	0.732 (0.445; 1.020)	<0.001	0.455 (0.130; 0.780)	0.01	0.638 (0.332; 0.945)	<0.001
Model 1	-0.003 (-0.251; 0.244)	0.98	0.390 (0.073; 0.708)	0.02	0.328 (-0.030; 0.686)	0.07	0.683 (0.359; 1.008)	<0.001
Model 2	-0.009 (-0.227; 0.260)	0.85	0.391 (0.074; 0.708)	0.02	0.344 (-0.015; 0.704)	0.06	0.682 (0.355; 1.009)	<0.001

[a] In mL/min/1.73 m^2 per year
Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S6b. Multiplicative interaction tests between baseline serum calcium (not albumin-corrected) and baseline eGFR in association with subsequent kidney function decline (95% CI)

	All patients (n=15755)	P*
Additional change in eGFR decline per each mg/dL higher calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Raw data	-0.008 (-0.018; -0.003)	0.16
Model 1	-0.009 (-0.015; -0.004)	0.08
Model 2	-0.009 (-0.015; -0.004)	0.08

Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S7a. Association between baseline corrected serum calcium and the subsequent rate of kidney function decline (95%-CI) in patients with baseline serum calcium within normal range (8.6-10.2 mg/dL)

	CKD 3a (*n*=8663)	P*	CKD 3b (*n*=3785)	P*	CKD 4 (*n*=1577)	P*	CKD 5 (*n*=386)	P*
Change in eGFR decline per each mg/dL higher albumin-corrected calcium (negative = extra decline)[a]								
Raw data	-0.302 (-0.681; 0.078)	0.12	0.547 (0.034; 1.055)	0.04	0.645 (0.120; 1.169)	0.02	0.649 (0.319; 0.978)	<0.001
Model 1	-0.229 (-0.614; 0.157)	0.25	0.286 (-0.224; 0.796)	0.27	0.546 (-0.003; 1.094)	0.05	0.693 (-0.164; 1.551)	0.11
Model 2	-0.233 (-0.620; 0.154)	0.24	0.278 (-0.231; 0.787)	0.29	0.541 (-0.009; 1.091)	0.05	0.630 (-0.246; 1.507)	0.16

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S7b. Multiplicative interaction tests between baseline corrected serum calcium and baseline eGFR in its association with subsequent kidney function decline (95%-CI) in patients with baseline serum calcium within normal range (8.6-10.2 mg/dL)

	All patients (n=14411)	P*
Additional change in eGFR decline per each mg/dL higher albumin-corrected calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Raw data	-0.041 (-0.061; -0.022)	<0.001
Model 1	-0.039 (-0.058; -0.019)	<0.001
Model 2	-0.039 (-0.058; -0.019)	<0.001

Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S8a. Association between baseline corrected serum calcium and the subsequent rate of kidney function decline (95%-CI) in patients with at least 3 eGFR test available

	CKD 3a (*n*=4786)	P*	CKD 3b (*n*=2426)	P*	CKD 4 (*n*=1220)	P*	CKD 5 (*n*=395)	P*
Change in eGFR decline per each mg/dL higher albumin-corrected calcium (negative = extra decline)[a]								
Raw data	-0.072 (-0.338; 0.194)	0.60	0.476 (0.156; 0.797)	0.004	0.409 (0.064; 0.754)	0.02	0.648 (0.322; 0.973)	<0.001
Model 1	0.016 (-0.230; 0.263)	0.12	0.359 (0.039; 0.678)	0.03	0.318 (-0.043; 0.678)	0.08	0.680 (0.356; 1.003)	<0.001
Model 2	0.010 (-0.260; 0.281)	0.94	0.360 (0.041; 0.679)	0.03	0.335 (-0.026; 0.696)	0.07	0.681 (0.355; 1.007)	<0.001

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S8b. Multiplicative interaction tests between baseline corrected serum calcium and baseline eGFR in its association with subsequent kidney function decline (95%-CI) in patients with at least 3 eGFR test available

	All patients (n=8827)	P*
Additional change in eGFR decline per each mg/dL higher albumin-corrected calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Raw data	-0.018 (-0.030; -0.007)	0.002
Model 1	-0.017 (-0.028; -0.005)	0.004
Model 2	-0.017 (-0.028; -0.005)	0.003

Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S9a. Association between baseline corrected serum calcium and subsequent kidney function decline (95% CI) - not imputed data

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Change in eGFR decline per mg/dL increase in for albumin corrected calcium at baseline (negative = greater decline; positive = less decline)[a]								
Raw data	-0.098 (-0.362; 0.165)	0.47	0.515 (0.196; 0.835)	0.002	0.428 (0.084; 0.772)	0.015	0.649 (0.319; 0.978)	<0.001
Model 1	-0.108 (-0.194; 0.410)	0.48	0.328 (-0.037; 0.692)	0.08	0.262 (-0.150;0.676)	0.21	0.630 (0.285; 0.974)	<0.001
Model 2	0.011 (-0.524; 0.546)	0.97	0.364 (-0.187; 0.915)	0.20	0.499 (0.036; 0.963)	0.04	0.355 (0.109; 0.601)	0.01

[a] In mL/min/1.73 m^2 per year
Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S9b. Multiplicative interaction tests between baseline corrected serum calcium and baseline eGFR in association with subsequent kidney function decline (95% CI) - not imputed data

	All patients (n=15755)	P*
Additional change in eGFR decline per each mg/dL higher albumin-corrected calcium for each mL/min/1.73m^2 higher unit of eGFR (negative = smaller effect)		
Raw data	-0.021 (-0.032; -0.009)	<0.001
Model 1	-0.014 (-0.027; -0.002)	0.02
Model 2	-0.012 (-0.027; 0.003)	0.11

Model 1 adjusted for age, sex, blood pressure, DM, CVD serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

Supplementary Table S10. Cox proportional-hazards regression analysis of the association between baseline corrected serum calcium and the subsequent risk of sustained decline in GFR of >30% (95%-CI)

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Number events	547		451		438		158	
HR for having event per each mg/dL higher albumin-corrected calcium[a]								
Raw data	1.19 (0.98; 1.44)	0.08	0.90 (0.74; 1.10)	0.31	0.75 (0.62; 0.90)	0.003	0.79 (0.64; 0.97)	0.03
Model 1	1.06 (0.87; 1.29)	0.53	0.98 (0.81; 1.19)	0.86	0.83 (0.68; 1.02)	0.08	0.84 (0.68; 1.03)	0.09
Model 2	1.06 (0.87; 1.29)	0.54	0.98 (0.81; 1.18)	0.84	0.84 (0.68; 1.03)	0.09	0.82 (0.67; 1.01)	0.06

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

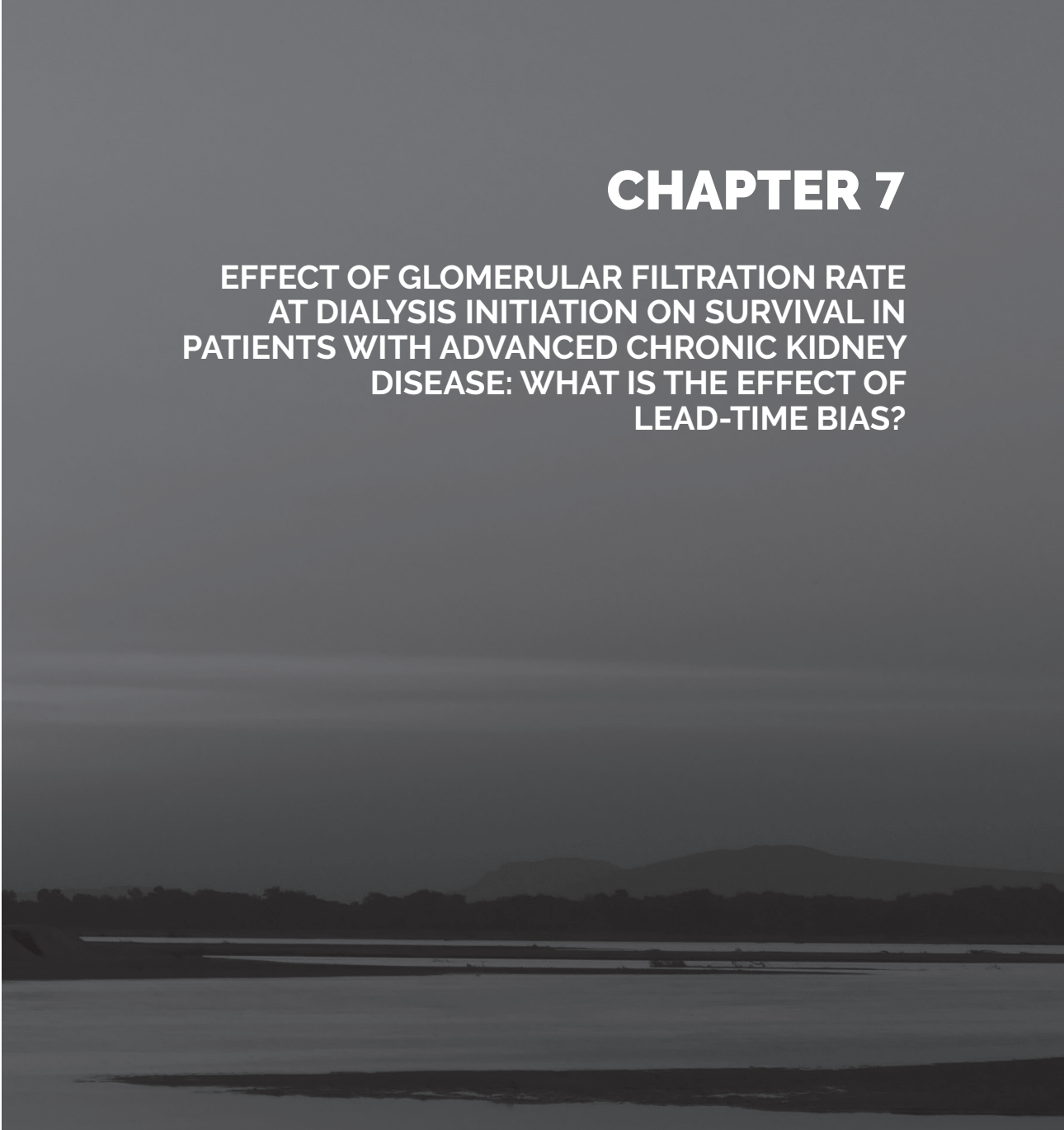
Supplementary Table S11. Cox proportional-hazards regression analysis of the association between baseline corrected serum calcium and the subsequent risk of RRT (95%-CI)

	CKD 3a (*n*=9286)	P*	CKD 3b (*n*=4190)	P*	CKD 4 (*n*=1784)	P*	CKD 5 (*n*=495)	P*
Number events	29		89		265		246	
HR for having event per each mg/dL higher albumin-corrected calcium[a]								
Raw data	0.89 (0.37; 2.14)	0.80	0.65 (0.40; 1.03)	0.07	0.62 (0.48; 0.79)	<0.001	0.92 (0.79; 1.07)	0.25
Model 1	0.81 (0.32; 2.00)	0.64	0.79 (0.51; 1.24)	0.31	0.74 (0.57; 0.95)	0.02	0.90 (0.78; 1.04)	0.16
Model 2	0.81 (0.33; 2.02)	0.65	0.79 (0.50; 1.22)	0.28	0.73 (0.57; 0.94)	0.02	0.87 (0.75; 1.00)	0.06

[a] In mL/min/1.73 m^2 per year.
Model 1 adjusted for baseline eGFR, age, sex, blood pressure, DM, CVD, serum albumin and hemoglobin
Model 2 adjusted for covariates in model 1 plus serum phosphorus, active vitamin D therapy and calcium supplements
*P-value for difference in the change in the rate of kidney function decline with one unit higher serum calcium

CHAPTER 7

EFFECT OF GLOMERULAR FILTRATION RATE AT DIALYSIS INITIATION ON SURVIVAL IN PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE: WHAT IS THE EFFECT OF LEAD-TIME BIAS?



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ABSTRACT

Purpose: According to current clinical guidelines, dialysis should be initiated based on uremic symptoms, often with a glomerular filtration rate (GFR) between 5 and 10 mL/min/1.73m^2. Little evidence exists about the optimal kidney function to start dialysis. Thus far, most observational studies have been limited by lead-time bias. Only a few studies accounted for lead-time bias, and showed contradictory results. We examined the effect of GFR at dialysis initiation on survival in chronic kidney disease patients, and the role of lead-time bias therein. We used both kidney function based on 24-hour urine collection (measured GFR[mGFR] and estimated GFR [eGFR]).

Materials and methods: A total of 1143 patients with eGFR data at dialysis initiation and 852 patients with mGFR data were included from the NECOSAD cohort. Cox regression was used to adjust for potential confounders. To examine the effect of lead-time bias, survival was either counted from the time of dialysis initiation or from a common starting point (GFR=20 mL/min/1.73m^2), using linear interpolation models.

Results: Without lead-time correction, no difference between early and late starters was present based on eGFR (hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.81-1.30). However, after lead-time correction, early initiation showed a survival disadvantage (HR between 1.10 [95% CI 0.82-1.48] and 1.33 [95% CI 1.05-1.68]). Based on mGFR, the potential survival benefit for early starters without lead-time correction (HR 0.80 [95% CI 0.62-1.03]) completely disappeared after lead-time correction (HR between 0.94 [95% CI 0.65-1.34] and 1.21 [95% CI 0.95-1.56]). Dialysis start time differed about a year between early and late initiation.

Conclusion: Lead-time bias is not only a methodological problem but has also clinical impact when assessing the optimal kidney function to start dialysis. Therefore, lead-time bias is extremely important to correct for. Taking account of lead-time bias, this controlled study showed that early dialysis initiation (eGFR >7.9; mGFR >6.6 ml/min/1.73m^2) was not associated with an improvement in survival. Based on kidney function, this study suggests that in some patients dialysis could be started even later than an eGFR<5.7 and mGFR <4.3 ml/min/1.73m^2.

INTRODUCTION

Current clinical KDIGO (Kidney Disease: Improving Global Outcomes) guidelines state that dialysis should be initiated based on uremic signs and symptoms.[1] This often occurs with a glomerular filtration rate (GFR) between 5 and 10 mL/min/1.73m^2. There is little evidence about the optimal kidney function to start dialysis and the only randomized study so far showed no effect on survival for starting at a GFR around 9.0 versus 7.2 mL/min/1.73m^2.[2] Several observational studies have been performed with contradictory results. Some studies suggested better survival for patients who started with a high plasma creatinine-based estimated GFR (eGFR), whereas the majority suggested better survival for those who started with a lower eGFR.[3-19] However, only four of these studies did properly account for lead-time bias, including our previous study by Korevaar et al.[5, 6, 10, 18] Nevertheless, all were based on a relatively low number of dialysis patients.

Lead-time bias often occurs when evaluating the efficacy of a treatment in observational studies, especially in dialysis initiation, and stems from a difference in timing of treatment initiation.[20] Specifically, lead-time is the added time of survival attributable to the fact that a selected group of patients starts earlier with dialysis than a later-starting comparative group. When comparing survival time starting from treatment initiation, early starters will show a survival benefit (Figure 1). Any potential survival benefit of early dialysis initiation may then be due to lead-time bias instead of representing an improvement in the course of the disease and effect on survival. In the IDEAL-study[2], in which lead-time bias is no issue due to randomization, no difference was observed in survival rates associated with a time difference of 6 months between early and late start. However, this randomized controlled trial (RCT) does not help to set the optimal kidney function to initiate dialysis. Furthermore, RCTs are hard to conduct and time-consuming, thus we are still bound to observational studies.

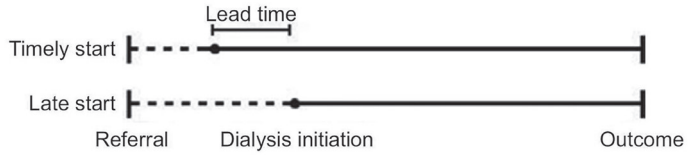

Figure 1. Lead time depending on moment of referral and time of dialysis initiation.
Notes: Lead-time bias tends to favor earlier dialysis initiation because patients starting dialysis with more residual kidney function enter dialysis earlier in the course of the disease, than those starting dialysis with less residual function and accordingly gain a spurious residual lifetime advantage. Analyzing survival from the moment of referral solves the problem of lead-time bias, as would analyzing from the moment a certain GFR is reached (e.g., 20 mL/min/1.73m^2 as used in the present study).

Interpretation of results is further complicated since most studies used only eGFR instead of true measurements of kidney function.[6] It has been argued that eGFR is less valid because of artificial low plasma creatinine levels in patients with fluid overload or low muscle mass, especially in low ranges of kidney function when initiation of dialysis is near.[21,22] Kidney function may be better reflected by the mean of the measured creatinine and urea clearance ($C_{Cr\text{-}U}$) based on 24-h urine collections (measured GFR [mGFR] by $C_{Cr\text{-}U}$). This study aims to examine the effect of kidney function (both eGFR and mGFR) at dialysis initiation on survival in CKD patients, and the role of lead-time bias therein.

MATERIAL AND METHODS

Study design

The Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD) is a multicenter, prospective observational cohort study in which 38 dialysis centers throughout the Netherlands participated.[23] Inclusion of patients took place between 1997 and 2007 and follow-up data on death were available until February 2015. Patients were followed until time of death or censored due to kidney transplantation, recovery of kidney function as reason to stop with dialysis therapy, withdrawal from the study, transfer to a dialysis center that did not participate in the study, loss to follow-up or end of the study period (February 2015), whichever came first. Available data on mGFR and eGFR during the pre-dialysis period, collected from medical records, were added retrospectively to the prospective NECOSAD cohort for a convenient sample of patients included before 2003. The study was approved for all participating hospitals by the Medical Ethics Committee of the Academic Medical Center in Amsterdam, as coordinating center of the NECOSAD study, and all these hospitals (Supplementary material) approved participation. The study was conducted according to the declaration of Helsinki. All patients gave written informed consent.

Patient inclusion

For the present analysis, incident dialysis patients of ≥18 years with no history of renal replacement therapy (RRT, i.e. starting dialysis or renal transplantation) were included at the start of dialysis treatment. Patients were excluded when they had a hemodialysis catheter. The latter ensured we excluded patients with acute renal impairment. The current study population includes the patients studied by Korevaar et al.[5]

Exposure and outcome

The effect of GFR at dialysis initiation on survival in CKD patients was investigated using time to death as outcome. The GFR at dialysis initiation was based on tertiles of GFR at the moment of dialysis initiation and included the categories late, intermediate and early dialysis initiation (i.e. low, intermediate and high levels of GFR). Starting groups were based on two measures: mGFR (ml/min/1.73m^2, by $C_{Cr\text{-}U}$) and eGFR (ml/min/1.73m^2). The first is calculated by the mean of endogenous $C_{Cr\text{-}U}$ in 24-h collected urine, corrected for body surface area, and the latter was calculated by the 4-item Modification of Diet in Renal Disease (MDRD) formula (Supplementary material).[24] The plasma creatinine concentration was measured per dialysis centre using the local method, which was predominately the alkaline picrate (Jaffe) method. A pilot study comparing these measurements with more precise enzyme-mediated methods found that the differences were negligible for the very high concentrations present in patients with end stage renal disease. For all patients included in the present analysis, the start date of dialysis was regarded as baseline. The GFR value at dialysis initiation was used as baseline measurement. For eGFR, the plasma creatinine was drawn before the first dialysis session. For mGFR, urine and blood samples were collected either before or until one month after the first dialysis session.[23]

Estimating kidney function decline for lead-time bias correction

Lead-time correction was achieved by using two approaches: mean annual decline rate of kidney function, and individual decline rates imputed from data available for a subgroup in NECOSAD. Both approaches were used to estimate the date when individuals would have had a specific predetermined GFR level before dialysis start (i.e. GFR 20 ml/min/1.73m^2). Survival time was then counted from this date onwards, thereby eliminating the added survival time associated with starting dialysis early, when counting survival time from dialysis initiation. For the first approach, we used average annual rates of kidney function decline for eGFR and mGFR in the year prior to dialysis initiation based on pre-dialysis data from the Dutch PREdialysis PAtient REcord-1 (PREPARE-1) study.[25-27] PREPARE-1 is a Dutch retrospective follow-up study with incident pre-dialysis patients with CKD stages 4-5 (for more details, see Supplementary material). PREPARE-1 and NECOSAD were performed during the same period.

Statistical analyses

Data are presented as mean values with standard deviations or median with interquartile ranges for continuous variables, depending on the distribution. Categorical variables are presented as numbers and percentages. P-values are two-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 20.

Missing values of potential confounders were imputed with multiple imputation methods using a fully conditional specification with 10 repetitions.[28-30] All available baseline variables and the outcome were used for imputation. Follow-up time was logarithmically transformed; age, baseline GFR values and BMI were square root transformed before entering in the imputation model. Estimates and standard deviations were calculated in each imputation set; pooled into one overall estimate and standard deviation according to Rubin's rules.[31, 32]

Kidney function decline

Individual kidney function declines prior to dialysis initiation were calculated following the two approaches as described earlier. For the first approach, average annual eGFR/mGFR rates from PREPARE-1, used for lead-time correction, were based on calculated individual annual GFR rates using linear regression. The assumption of a linear decline is considered safe, given the relatively short follow-up period of one year. At least two GFR measurements had to be available to estimate the rate of decline. Furthermore, a minimum of 30 days between the first and last pre-dialysis GFR values was applied as a too short time frame would give an unreliable estimation of the decline. For the second approach, individual annual GFR decline rates prior to dialysis initiation were first calculated for those individuals in NECOSAD with available pre-dialysis GFR data, also linear regression analysis was used for this purpose. With these available pre-dialysis GFR decline data, GFR decline rates were imputed for individuals with missing pre-dialysis data in NECOSAD.

Survival analysis

In our cohort of NECOSAD, we first performed a regular survival analysis for the effect of GFR at dialysis initiation on survival from dialysis initiation. Cumulative survival rates for early, intermediate and late starters were calculated using the Kaplan-Meier method. Crude and adjusted hazard ratios for timing of dialysis initiation were obtained using Cox proportional hazard regression analyses, adjusted for the confounders age, sex, primary kidney diseases, ethnicity, and comorbidities using the Khan comorbidity score.[33] The Khan comorbidity score includes the following risk groups: low risk is defined as age < 70 years and no comorbid illness; medium risk is defined as age 70-80 years or age < 80 years with any one of the following: cardiac, pulmonary or liver disease or age < 70 years with diabetes mellitus; high risk is defined as age > 80 years or any age with two or more organ dysfunctions in addition to end-stage renal disease or any age with visceral malignancy.[33] Information on comorbidities included in the Khan score was collected by using questionnaires completed by clinicians and was based on clinical diagnosis and information on comorbidities from patient records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[34]

Survival analysis, corrected for lead-time bias

Next, aforementioned survival analyses were repeated with correction for lead-time bias. This was achieved by measuring survival from the predetermined point before dialysis (ie, eGFR/mGFR of 20 ml/min/1.73m^2) rather than from the start of dialysis (Figure 1), based on the method used by Traynor et al.[18] The date of this common starting point was calculated back from the start of dialysis, using a linear interpolation model with either the previously computed mean annual GFR slopes prior to dialysis commencement from PREPARE-1 or the computed individual pre-dialysis GFR slopes from NECOSAD. Then, these lead-time corrected results were compared to the previous uncorrected results of survival analyses. The difference in hazard ratios between survival rates for the timing of dialysis initiation, corrected and uncorrected for lead-time bias, showed the impact of lead-time bias. Finally, the length of lead-time was estimated by calculating the difference in baseline GFR value between early versus late and intermediate versus late dialysis initiation, divided by the annual GFR decline from PREPARE-1.

Sensitivity analyses

To validate the robustness of our results, we performed several sensitivity analyses. First, to confirm that early starters do not decline faster than late starters, mean GFR decline rates prior to dialysis initiation were calculated for late-, intermediate- and early-starting groups in both PREPARE-1 and a selection of patients in NECOSAD, with available data on GFR decline rates prior dialysis initiation. Early-, intermediate- and late-starting groups were based on the same GFR tertiles as used in the main analyses in NECOSAD. Second, correction for lead-time bias was also achieved by using the lowest and highest value of decline in kidney function extracted from review of the literature on the GFR decline in the year prior to dialysis initiation.[23, 35, 36] Third, we repeated the analyses in subjects with both an mGFR and eGFR value at dialysis initiation available to enable a direct comparison between mGFR and eGFR results. Fourth, we varied the cut-off point of the GFR value for dividing the study population into three categories. Fifth, we performed additional adjustment in the survival analysis for possible additional confounders or variables that are potentially in the causal pathway: smoking, systolic and diastolic blood pressure, and blood pressure medication.

RESULTS

Patient characteristics at baseline

In total, 852 patients with a mGFR measurement and 1143 patients with an eGFR measurement at dialysis initiation were included for the present analyses. See Figure 2 for a flow chart of patient inclusion. Individual pre-dialysis decline rates were available for 150 of the 852 patients with mGFR data and for 363 of the 1143 patients with eGFR data. Baseline characteristics for the total population under study and for early, intermediate and late starters, either based on mGFR or eGFR data, are shown in Table 1. Mean baseline mGFR was 2.5 (±1.4) for late starters, 5.4 (±0.7) for intermediate and 8.9 (±2.1) ml/min/1.73m^2 for early starters. Late, intermediate and early starters based on eGFR data had higher mean baseline eGFRs of 4.4 (±1.2), 6.7 (±0.6), and 10.2 (±2.3) ml/min/1.73m^2, respectively. Median time from dialysis initiation and baseline plasma creatinine measurement used to calculate eGFR was 6 (interquartile range 1-14) days. In general, diabetes was the underlying cause of kidney disease in a larger proportion of early starters compared to later starters. A total of 21 variables were used to impute the missing values of potential confounders at baseline for both mGFR and eGFR. Most confounders had no missing values; from the variables with missing values, the percentage of missing values varied between 0.5 and 11.2%.

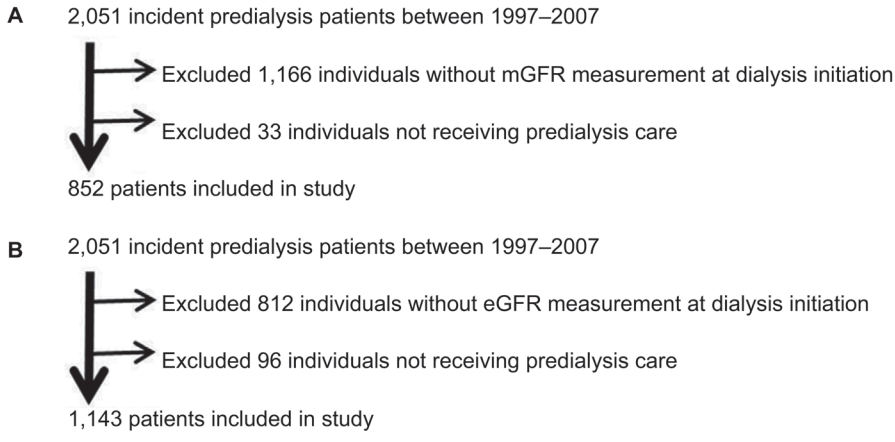

Figure 2. Patient inclusion flowchart for patients with data on mGFR (A) and data on eGFR (B).
Abbreviations: mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate.

Table 1. Patients characteristics table

		Moment of dialysis initiation – mGFR				Moment of dialysis initiation – eGFR		
	Total n=852	Late n=284	Intermediate n=284	Early n=284	Total n=1143	Late n=381	Intermediate n=381	Early n=381
Baseline GFR (ml/min/1.73 m²)	5.6 (±3.0)	2.5 (±1.4)	5.4 (±0.7)	8.9 (±2.1)	7.1 (±2.8)	4.4 (±1.2)	6.7 (±0.6)	10.2 (±2.3)
Age (year)	61.1 (47.9; 70.6)	62.1 (47.8; 71.7)	61.8 (49.1; 70.8)	59.0 (47.1; 69.1)	62.0 (50.0; 71.3)	58.3 (46.3; 67.9)	62.5 (50.8; 72.0)	66.3 (54.3; 74.3)
Sex (% man)	527 (61.9)	171 (60.2)	176 (62.0)	180 (63.4)	716 (62.6)	201 (52.8)	240 (63.0)	275 (72.2)
Ethnicity Caucasian (%)	761 (92.1)	255 (90.7)	258 (93.5)	248 (92.2)	1039 (90.9)	339 (89.0)	349 (91.6)	351 (92.1)
BMI (kg/m²)	24.4 (22.1; 27.4)	24.1 (22.0; 26.9)	24.4 (22.2; 27.3)	24.8 (22.3; 28.2)	24.5 (22.2; 27.3)	24.4 (22.0; 27.5)	25.0 (22.7; 27.2)	24.0 (21.9; 27.1)
Smoker (%)	195 (23.8)	62 (22.7)	68 (23.9)	65 (23.8)	238 (23.4)	76 (21.7)	81 (24.3)	81 (24.5)
Primary Kidney disease (%)								
Diabetes mellitus	128 (15.0)	45 (15.8)	32 (11.3)	51 (18.0)	170 (14.9)	37 (9.7)	57 (15.0)	76 (19.9)
Glomerulonephritis	110 (12.9)	36 (12.7)	42 (14.8)	32 (11.3)	142 (12.4)	60 (15.7)	45 (11.8)	37 (9.7)
Renal vascular disease	143 (16.8)	57 (20.1)	41 (14.4)	45 (15.8)	182 (15.6)	59 (15.5)	43 (11.3)	80 (21.0)
Other	471 (55.3)	146 (51.4)	169 (59.5)	156 (54.9)	649 (56.8)	252 (59.1)	236 (61.9)	188 (49.3)
Khan index (%)								
Low	366 (43.0)	113 (39.8)	140 (49.3)	113 (39.8)	474 (41.5)	212 (55.6)	158 (41.5)	104 (27.3)
Medium	280 (32.9)	102 (35.9)	77 (27.1)	101 (35.6)	374 (32.7)	107 (28.1)	134 (35.2)	133 (34.9)
High	206 (24.2)	69 (24.3)	67 (23.6)	70 (24.6)	295 (25.8)	62 (16.3)	89 (23.4)	144 (37.8)
Medication								
Ace inhibitors	144 (16.9)	42 (14.8)	43 (15.1)	59 (20.8)	199 (17.4)	56 (14.7)	72 (18.9)	71 (18.6)
Calcium antagonist	180 (21.1)	43 (15.1)	56 (19.7)	81 (28.5)	280 (24.5)	91 (23.9)	102 (26.8)	87 (22.8)
Beta blockers	159 (18.7)	45 (15.8)	50 (17.6)	64 (22.5)	262 (22.9)	87 (22.8)	92 (24.1)	83 (21.8)
Diuretics	167 (19.6)	40 (14.1)	59 (20.8)	68 (23.9)	273 (23.9)	68 (17.8)	104 (27.3)	101 (26.5)

	Moment of dialysis initiation – mGFR				Moment of dialysis initiation – eGFR			
	Total n=852	Late n=284	Intermediate n=284	Early n=284	Total n=1143	Late n=381	Intermediate n=381	Early n=381
Systolic blood pressure (mmHg)	149.8 (±23.8)	150.7 (±24.7)	150.3 (±22.7)	148.4 (±24.0)	150.0 (±24.1)	150.7 (±24.6)	151.6 (±24.1)	147.7 (±23.5)
Diastolic blood pressure(mmHg)	83.8 (±23.8)	83.9 (±13.8)	85.7 (±12.8)	81.8 (±11.8)	82.9 (±12.8)	85.3 (±13.5)	83.7 (±11.7)	79.6 (±12.5)
Dialysis modality (% HD)*	437 (51.3)	167 (58.8)	136 (47.9)	134 (47.2)	687 (60.1)	218 (57.2)	222 (58.3)	247 (64.8)

Notes: Continuous variables presented as means (± standard deviation) or medians (interquartile range) depending on distribution; categorical variables as frequencies, and percentages. Late-, intermediate-, and early-starting groups are based on tertiles of GFR values at the moment of dialysis initiation.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated, glomerular filtration rate; GFR, glomerular filtration rate; HD, hemodialysis; mGFR, measured glomerular filtration rate.

Survival analyses with and without lead-time correction

Using the first approach, for the starting groups based on mGFR data, an unadjusted Kaplan-Meier analysis suggested an incrementally increased survival of early starters compared to late starters without lead-time correction (Figure 3A). However, after correction for lead-time bias the Kaplan-Meier analysis suggested a reversed survival benefit of patients initiating dialysis later (Figure 3B). These analyses were also performed for starting groups based on eGFR data. In contrast, without lead-time correction an increased cumulative survival was observed for late starters (Figure 3C) and after correction for lead-time bias this survival benefit increased (Figure 3D). These results were reflected by the crude Cox analyses, with and without correction for lead-time bias, as shown in Table 2.

Table 2. Effect of GFR at dialysis initiation on survival and length of lead time

	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Length of lead-time[b]
Data on mGFR			
Without correction for lead-time			
Late starters (<4.3)	Ref	Ref	
Intermediate starters (4.3-6.6)	0.86 (0.67; 1.10)	1.00 (0.77; 1.28)	
Early starters (>6.6)	0.79 (0.61; 1.02)	0.80 (0.62; 1.03)	
With correction for lead-time			
Late starters	Ref	Ref	
Intermediate starters	1.02 (0.80; 1.31)	1.23 (0.95; 1.58)	6.3
Early starters	1.14 (0.88; 1.47)	1.21 (0.93; 1.56)	13.9
Data on eGFR			
Without correction for lead-time			
Late starters (<5.7)	Ref	Ref	
Intermediate starters (5.7-7.9)	1.21 (0.96; 1.53)	1.02 (0.80; 1.29)	
Early starters (>7.9)	1.55 (1.24; 1.94)	1.03 (0.81; 1.30)	
With correction for lead-time			
Late starters	Ref	Ref	
Intermediate starters	1.33 (1.06; 1.69)	1.12 (0.88; 1.42)	3.6
Early starters	1.97 (1.58; 2.47)	1.33 (1.05; 1.68)	9.2

Note: [a] Adjusted for age, sex, Khan comorbidity score, primary kidney diseases, and ethnicity; b length of lead time (months) = Δbaseline GFR/annual GFR slope from PREPARE-1, eg, length of lead time for early versus late starters based on mGFR data = (8.9–2.5)/5.5=13.9 months.
Abbreviations: GFR, glomerular filtration rate; HR, hazard ratio; CI, confidence interval; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate.

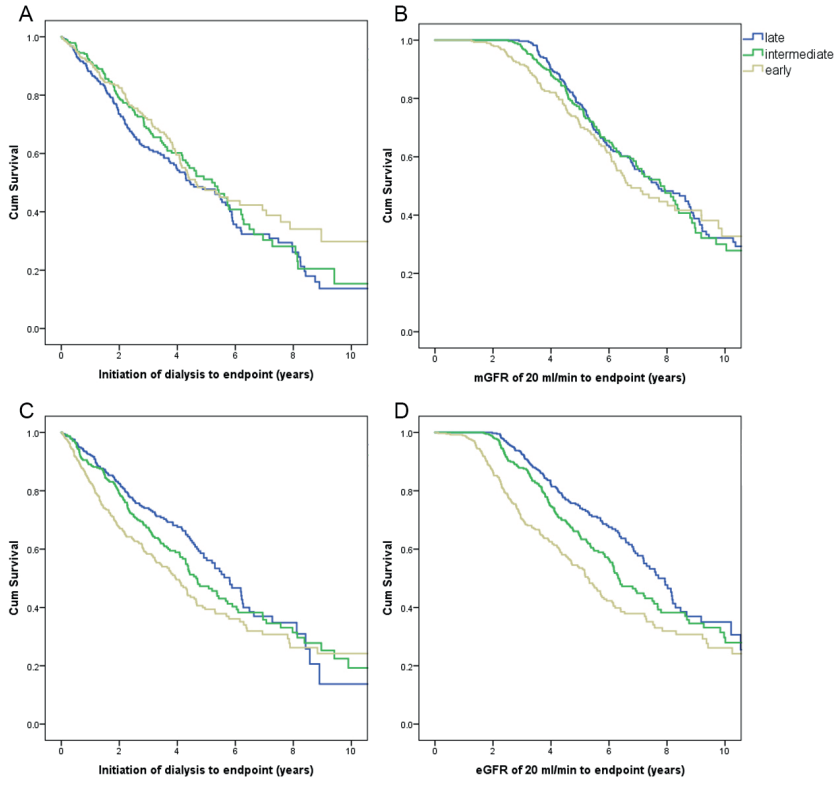

Figure 3. Kaplan-Meier survival curves for late, intermediate and early starters.
Notes: mGFR (A, B) and eGFR (C, D), either from dialysis initiation (A, C) or from a GFR value of 20 mL/min/1.73 m^2 (B, D).
Abbreviations: mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate.

In the adjusted Cox analyses based on mGFR data, both intermediate and early starters had a lower risk of death compared to late starters, with HRs of 1.00 (0.77-1.28, early) and 0.80 (0.62-1.03, late). When corrected for lead-time bias, an inverse association was present with HRs of 1.23 (0.95-1.58) and 1.21 (0.93-1.56) for intermediate and early starters versus late starters, respectively (Table 2). In contrast, this observed inverse association of adjusted HRs after correction for lead-time was not found for starting groups based on eGFR data at dialysis initiation. Without lead-time bias correction, the adjusted Cox analyses based on eGFR data at dialysis initiation, showed no difference in mortality risk between early and late dialysis initiation. However, after correction for lead-time bias the early starters had a higher risk of death, with an HR of 1.33 (1.05-1.68) (Table 2). Using the second approach with individual decline rates prior to dialysis initiation from NECOSAD to correct for lead-time bias, the adjusted Cox analyses based on mGFR data showed no substantial difference between early

and late starters (Table 3). The hazard ratio was approximately equal to 1. Based on eGFR data, the early and intermediate starters still had a higher risk of death compared to late starters after correction for lead-time bias, with an HR of 1.10 (0.81-1.50) and 1.10 (0.82-1.48) (Table 3), respectively.

Table 3. Effect of GFR at dialysis initiation on survival and length of lead-time

	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Length of lead-time[b]
Data on mGFR			
With correction for lead-time			
Late starters (<4.3)	Ref	Ref	
Intermediate starters (4.3-6.6)	0.90 (0.64; 1.28)	0.92 (0.65; 1.31)	6.8
Early starters (>6.6)	0.90 (0.65; 1.26)	0.94 (0.65; 1.34)	25.6
Data on eGFR			
With correction for lead-time			
Late starters (<5.7)	Ref	Ref	
Intermediate starters (5.7-7.9)	1.35 (1.01; 1.80)	1.10 (0.81; 1.20)	5.1
Early starters (>7.9)	1.72 (1.29; 2.28)	1.10 (0.82; 1.48)	14.5

Notes: [a] Adjusted for age, sex, Khan comorbidity score, primary kidney diseases, and ethnicity; [b] length of lead time (months) = Δbaseline GFR/annual GFR slope from NECOSAD, eg, length of lead time for early versus late starters based on mGFR data = (8.9–2.5)/3=25.6 months.
Abbreviations: GFR, glomerular filtration rate; HR, hazard ratio; CI, confidence interval; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; NECOSAD, Netherlands Cooperative on the Adequacy of Dialysis-2

Length of lead-time

Using the first approach with the computed annual GFR declines derived from the pre-dialysis cohort PREPARE-1, as shown in Table 4, yielded a length of lead-time of 13.9 months for early versus late starters and 6.3 months for intermediate versus late starters, based on mGFR data (Table 2). For starting groups based on eGFR data, a shorter length of lead-time of 9.2 and 3.6 months was shown for early versus late and intermediate versus late starting groups, respectively (Table 2). Using the second approach, with individual decline rates from NECOSAD to correct for lead-time bias, even longer lengths of lead-time were calculated for early and intermediate versus late starters, both based on mGFR and eGFR data (Table 3). Mean rates of kidney function decline for the three starting groups, used to compute the length of lead-time based on the second approach, are shown in Table 5.

Table 4. Rates of kidney function decline in PREPARE-1

	PREPARE-1
N	211
Rate of mGFR decline (mL/min/1.73m²/y)	-5.5 (±6.4)
mGFR value at dialysis initiation	6.2 (±1.9)
N	336
Rate of eGFR decline (mL/min/1.73m²/y)	-7.6 (±8.9)
eGFR value at dialysis initiation	8.3 (±4.1)

Notes: Decline rates shown are means (± standard deviation).
Abbreviations: mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; PREPARE-1, PREdialysis PAtient REcord-1.

Table 5. Rates of kidney function decline in NECOSAD

		Mean decline rate NECOSAD (mL/min/1.73m²/y)
	Late starters	-7.4 (±12.0)
mGFR	**Intermediate starters**	-5.1 (±11.7)
	Early starters	-3.0 (±12.7)
	Late starters	-5.6 (±9.4)
eGFR	**Intermediate starters**	-5.4 (±9.4)
	Early starters	-4.8 (±10.5)

Notes: Decline rates shown are means (± standard deviation).
Abbreviations: mGFR, measured glomerular filtration rate; eGFR, estimated GFR; NECOSAD, Netherlands Cooperative on the Adequacy of Dialysis-2.

Sensitivity analyses

The calculated annual GFR declines prior to dialysis initiation in PREPARE-1 and a selection of patients of NECOSAD-II (with available data) showed that early/intermediate starters had a less rapid decline then late starters (Table S1). Repeating the crude and adjusted Cox analyses with correction for lead-time bias based on the lowest and highest value of GFR decline extracted from literature, the adjusted and corrected risk of mortality for early compared to late starters ranged between 1.14 (0.88-1.47) and 1.61 (1.24-2.09), based on mGFR data (Table 6). This was accompanied by a length of lead-time between 11.5 and 23.6 months. For starting groups based on eGFR values, an adjusted and corrected HR between 1.22 (0.96-1.54) and 1.52 (1.21-1.92) was calculated for early versus late dialysis initiation, accompanied by a length of lead-time ranging from 6.0 to 15.3 months (Table 6).

Additional subgroup analyses in subjects (N=577) with both an eGFR and mGFR measurement available at dialysis initiation were similar and in line with results obtained in the main analyses. The classification between late, intermediate and early starters was tested by additional analyses in which the study population was divided into two groups based on the median GFR value at dialysis initiation, in quartiles, and in categories of GFR value at dialysis initiation <5, 5-10, >10 ml/min/1.73m^2 (data not shown). All classifications showed the same patterns of association and confirmed the stability of our results. Adding additional confounders to the Cox proportional hazards model did not alter our conclusions (Table S2).

Table 6. Effect of GFR at dialysis initiation on survival and length of lead-time based on literature search

	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Length of lead-time[b]
Data on mGFR			
With correction for lead-time based on			
Lowest value in literature (-3.2[y])			
Late starters	Ref	Ref	
Intermediate starters	1.14 (0.89; 1.47)	1.40 (1.09; 1.81)	10.9
Early starters	1.48 (1.15; 1.90)	1.61 (1.24; 2.09)	23.6
Highest value in literature (-6.6[y])			
Late starters	Ref	Ref	
Intermediate starters	0.99 (0.78; 1.28)	1.19 (0.93; 1.54)	5.3
Early starters	1.08 (0.84; 1.39)	1.14 (0.88; 1.47)	11.5
Data on eGFR			
With correction for lead-time based on			
Lowest value in literature (-4.7[y])			
Late starters	Ref	Ref	
Intermediate starters	1.40 (1.11; 1.77)	1.8 (0.93; 1.49)	5.9
Early starters	2.25 (1.79; 2.81)	1.52 (1.21; 1.92)	15.3
Highest value in literature (-12.1[y])			
Late starters	Ref	Ref	
Intermediate starters	1.29 (1.02; 1.63)	1.08 (0.85; 1.37)	2.3
Early starters	1.81 (1.45; 2.27)	1.22 (0.96; 1.54)	6.0

Notes: [a] Adjusted for age, sex, Khan comorbidity score, primary kidney diseases, and ethnicity; [b] length of lead time (months) = Δbaseline GFR/annual GFR slope; [c] annual GFR decline (mL/min/1.73 m^2) in the year prior to dialysis initiation.

Abbreviations: GFR, glomerular filtration rate; HR, hazard ratio; CI, confidence interval; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate

DISCUSSION

This study on the effect of lead-time bias when examining the effect of both eGFR and mGFR at dialysis initiation on survival in CKD patients underlines the impact of lead-time bias herein. Without lead-time bias correction, we demonstrated no substantial effect of GFR levels at dialysis initiation, ie, early versus late start, on survival in CKD patients, although a borderline survival benefit for early dialysis initiation was observed based on mGFR. However, after lead-time correction early dialysis initiation yielded no survival benefit and seemed rather harmful, irrespective whether early start was based on eGFR or mGFR. The start time for dialysis differed about a year between early and late starters. Our results underline the importance to correct for lead-time bias and showed that early dialysis initiation was not associated with an improvement in survival.

To our knowledge, this is one of the first studies accounting for lead-time bias in survival of CKD patients starting dialysis in an observational study design, based on both eGFR and mGFR. The only performed RCT, in which lead-time is no issue, showed no difference between early and late initiation strategies.[2] However, in this RCT the mean difference in eGFR between early and late starters was only 2.2 mL/min/1.73m^2 with 6 months difference in dialysis start time, whereas we showed a difference in eGFR of 5.8 mL/min/1.73m^2 with 9.2-14.5 months of lead-time. Our data based on individual lead-time correction for eGFR data supports the conclusion of the IDEAL trial that early dialysis initiation was not associated with an improvement in survival.[2] Besides, several observational studies have also investigated the effect of GFR at dialysis initiation on survival in CKD dialysis patients, with contradictory results. Some studies suggested better survival for patients who started dialysis early, whereas most studies suggested better survival for those who started late and most studies did not take into account lead-time bias.[3-19] In the latter case, lead-time bias cannot explain their findings, because lead-time bias can only explain better survival for early starters. However, of these previous studies, only four have taken account of lead-time bias, but were never based on both eGFR and mGFR and had small study populations.[5, 6, 10, 18] One study was based on Kt/V measurements, which is beyond the scope of this article.[5] Our eGFR results confirmed the findings of the two studies based on eGFR: survival benefit in favor of late starters.[10, 18] With a larger sample size, the present study extends these results by showing a stronger association between late start and survival benefit when accounting for lead-time bias.

With regard to the mGFR results, only one other study also used mGFR and corrected for lead-time; showing a survival disadvantage for "late" starters.[6] However, in this Hong Kong

study, later starters were initial refusers, i.e. no real late starters, compared to elective starters (baseline of difference only 0.3 ml/min/1.73m^2) and they were in an initial worse condition upon starting dialysis. Therefore, these results were not comparable with our data. The relatively high percentage of patients with a low Khan score in this dialysis cohort, for both eGFR and mGFR, is in line with results in the article of Khan et al.[33] The pathophysiological mechanisms underlying the observed disadvantage of early starters remain unclear, but suggest harmful effects of the dialysis procedure itself.[37-40]

Our somewhat different findings between starting groups based on either eGFR or mGFR data could be explained by misclassification bias. Misclassification bias occurs when either outcome or exposure is misclassified, i.e. the probability for early starters to be misclassified as late starter or vice versa. This type of bias is present with calculating eGFR based on the MDRD formula, and is almost completely eliminated using mGFR, which is not influenced by muscle mass.[8, 21, 41] For instance, frail or elderly patients with muscle wasting have lower levels of plasma creatinine, resulting in falsely high eGFR levels compared to their true underlying kidney function. Therefore they are prone to be misclassified as early starter; the opposite applies for late starters.[42, 43] In addition, eGFR overestimates kidney function in advanced CKD, as reflected by our higher values for the eGFR than mGFR starting groups.[21, 44] As a consequence, misclassification bias overestimates survival in the late-initiation group of eGFR and underestimates the survival in early starters. Indeed, we demonstrated that the significant crude survival disadvantage for early versus late starters, in the eGFR group without lead-time correction, completely disappeared after adjustment for baseline confounders. Following this, misclassification bias could also explain the observed differences in adjusted mortality risks for early versus late starters when comparing mGFR and eGFR. In addition, plasma creatinine measurements in the present study were not always performed on standardized plasma creatinine assays, which theoretically could lead to imprecision of eGFR measurements, besides the introduced misclassification bias, due to the influence of muscle mass on eGFR measurements. mGFR seems more accurate in decision-making on timing of dialysis initiation; when eGFR is used a thorough realization of its weaknesses and pitfalls is needed.

The present study has potential limitations. First, we cannot rule out the presence of confounding by indication, resulting from clinical decision-making at dialysis initiation. Although adjustment for a range of known confounders did not affect the results, we did not have information on uremic symptoms.[17, 45-48] Therefore, residual confounding could not be completely eliminated. Second, a mean annual GFR decline was used based on a selected group of patients with pre-dialysis measurements from PREPARE-1. For both of these limitations, one might have

concerns that early starters with or without uremic symptoms might have a faster decline in kidney function with worse prognosis, than later starters. However, in the current study this is no limitation, since the opposite holds true for starting groups in PREPARE-1 and available data in NECOSAD. Furthermore, our results, ie, based on decline rates derived from PREPARE-1, fell within the observed range based on available literature, which justified the use of the decline rates from PREPARE-1. Finally, we also used imputed individual GFR declines based on patients with available pre-dialysis data in NECOSAD. Third, survivor bias (ie, immortal time bias) could be a potential limitation of addressing lead-time bias in this way, as individuals that died before starting dialysis are not included in our cohort. Only people who survived to the time of dialysis initiation were analyzed, excluding those who died before starting dialysis. As a consequence, the individuals included in the present study will have a better survival in general. Therefore, survival rates could be overestimated in the present results, especially for late starters. The difference in survival rates between early and late starters could partially be explained by survivor bias. However, we corrected for health status by adjusting for several confounders, such as Khan's score and age. Therefore, we consider the influence of survivor bias as minimal and will not alter the conclusion. However, pre-dialysis drop-out due to death was limited to 11% over the complete follow-up period in the PREPARE-1 study.[25, 26] Finally, the mGFR values could be not completely accurate, since they are on 24h-urine collections. However, any errors are assumed to be randomly distributed over the study population and would dilute the effect.

Major strengths of our study are that we were able to eliminate lead-time bias in an observational cohort study design and that we assessed the long-term effect of both eGFR and mGFR at dialysis initiation on survival (until 18 years of follow-up). Our results clearly indicate the importance to correct for lead-time bias.

Our results could have impact on the currently used KDIGO guideline for decision-making on timing of dialysis initiation, which states that dialysis should be initiated based on uremic signs and symptoms, often in the eGFR range between 5- 10 mL/min/1.73m^2.[1] However, considering this eGFR range, early initiation (ie, >7.9 mL/min/1.73m^2) shows a clear mortality disadvantage in the current study when lead-time is accounted for. Furthermore, data on mGFR could be added in the guideline. In context of misclassification of patients in eGFR early starting groups, mGFR may be more reliable as guide for timing of dialysis initiation.[22] While the IDEAL study showed that the strategy to initiate dialysis with a mean eGFR <7.2 ml/min/1.73m^2 is safe, we show that, based on solely kidney function, in some patients we can even go lower than an eGFR of 5.7 and a mGFR of 4.3 mL/min/1.73m^2.[2] Further research is needed to examine this

precise kidney function threshold and to implement these findings in context of presence of uremic symptoms and quality of life.

CONCLUSION

We showed that lead-time bias is not only a methodological problem, but also a clinical problem when assessing the optimal kidney function to start dialysis. Therefore, lead-time bias is extremely important to correct for. Taking account of lead-time bias, this controlled study showed that early dialysis initiation (i.e. eGFR >7.9, mGFR >6.6 ml/min/1.73m^2) was not associated with an improvement in survival. Based solely on kidney function, this study suggests that in some patients dialysis could be started even later than an eGFR <5.7 and mGFR <4.3 ml/min/1.73m^2. These results should naturally be interpreted in the context of clinical judgment and presence of any symptoms.

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SUPPLEMENTARY MATERIAL

Hospitals in the NECOSAD study

Maasstad Hospital Rotterdam, Deventer Hospital Deventer, Sint Lucas Andreas Hospital Amsterdam, Academic Medical Center Amsterdam, Maxima Medical Center Veldhoven, Catharina Hospital Eindhoven, Medical Center Haaglanden Den Haag, University Medical Center Groningen, Kennemer Gasthuis Haarlem, Atrium Medical Center Heerlen, Medical Center Leeuwarden, Leiden University Medical Center Leiden, Elisabeth Hospital Tilburg, University Medical Center Utrecht, Antonius Ziekenhuis Nieuwegein, Hospital Gelderse Vallei Ede, Haga Hospital Leyenburg Den Haag, Academic Hospital Maastricht, Jeroen Bosch Hospital Den Bosch, Medisch Spectrum Twente Enschede, Albert Schweitzer Hospital Dordrecht, Alysis Zorggroep Rijnstate Hospital Arnhem, Dianet Dialysis Center Lunetten Utrecht, Canisius Wilhelmina Hospital Nijmegen, Vie Curi Medical Center Venlo, Leveste Scheper Hospital Emmen, Dianet Dialysis Center Holendrecht Amsterdam, Haga Hospital Rode Kruis Den Haag, Rijnland Hospital Leiderdorp, Admiraal de Ruyter ziekenhuis Goes, Medical Center Alkmaar, Laurentius Ziekenhuis Roermond, Dialysis Center 't Gooi Hilversum, Groene Hart Hospital Gouda, Westfries Gasthuis Hoorn, TergooiHospitals Hilversum, Martini Ziekenhuis Groningen, Zaans Medical Center Zaandam.

Formulae

To calculate the eGFR we used the MDRD formula as stated below.

$$eGFR\ (mL/min/1.73\ m^2) = 186 * plasma\ creatinine/88.4^{-1.154} * age^{-0.203} * 0.742\ (if\ female) * 1.212\ (if\ African)$$

To calculate the mGFR based on 24-h urine samples we used the following calculation.

$$mGFR\ urea = urine\ urea\ (mmol/day) / plasma\ urea\ (mmol/l) * (1000/1440)$$
$$mGFR\ creatinine = urine\ creatinine\ (mmol/day) / (plasma\ creatinine\ (\mu mol/l) /1000) * (1000/1440)$$
$$mGFR\ urea\ and\ creatinine = (mGFR\ urea + mGFR\ creatinine) / 2$$

$$mGFR\ (mL/min/1.73\ m^2) = (mGFR\ urea\ and\ creatinine*1.73)*10000 / (weight^{0.424}\ (kg) * height^{0.725}\ (cm) * 71.84)$$

PREPARE-1

PREPARE-1[1-3] is a retrospective follow-up study of 500 consecutive incident pre-dialysis patients with chronic kidney disease (CKD) stages 4-5. These patients were treated in one of the outpatient clinics of 8 Dutch hospitals between 1999 and 2001. Patients had been referred to these outpatient clinics when creatinine clearance was below 20 ml/min. In addition, these patients were at least 18 years of age, had not had prior RRT and the need for RRT was expected within one year. The clinical course of pre-dialysis patients was followed through the medical charts until the start of dialysis, transplantation, death, loss to follow-up, or January 1, 2008, whichever came first.

Supplemental Table 1. Annual rates of kidney function decline prior dialysis initiation for late, intermediate and early starters with available data in PREPARE -1 and NECOSAD

	PREPARE-1		NECOSAD-II*	
	Number of patients	GFR decline (mL/min/1.73m²/y)	Number of patients	GFR decline (mL/min/1.73m²/y)
mGFR decline (mL/min/1.73m²/y)	N=211		N=150	
Late starters	29	-7.2 (±6.3)	11	-9.6 (±8.5)
Intermediate starters	96	-5.9 (±6.3)	55	-8.1 (±9.9)
Early starters	83	-4.5 (±6.4)	84	-3.6 (±11.3)
eGFR decline (mL/min/1.73m²/y)	N=336		N=363	
Late starters	73	-8.2 (±9.3)	78	-6.4 (±5.9)
Intermediate starters	109	-7.1 (±6.0)	104	-6.5 (±7.8)
Early starters	154	-7.7 (±10.3)	181	-7.2 (±11.8)

Notes: *Selection of patients with available data on GFR decline rates prior to dialysis initiation. Decline rates shown are mean (± standard deviation)

Abbreviations: GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; PREPARE-1, PREdialysis PAtient REcord-1; NECOSAD, Netherlands Cooperative on the Adequacy of Dialysis-2.

Supplemental Table 2. Effect of GFR at dialysis initiation on survival and length of lead-time

	Adjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]
Data on mGFR		
Without correction for lead-time		
Late starters (<4.3)	Ref	Ref
Intermediate starters (4.3-6.6)	0.97 (0.74; 1.25)	0.97 (0.75; 1.26)
Early starters (>6.6)	0.76 (0.59; 0.99)	0.76 (0.59; 0.99)
With correction for lead-time		
Late starters	Ref	Ref
Intermediate starters	1.21 (0.93; 1.57)	0.88 (0.61; 1.26)
Early starters	1.16 (0.89; 1.51)	0.91 (0.64; 1.31)
Data on eGFR		
Without correction for lead-time		
Late starters (<5.7)	Ref	Ref
Intermediate starters (5.7-7.9)	1.02 (0.80; 1.30)	1.02 (0.80; 1.30)
Early starters (>7.9)	0.99 (0.78; 1.25)	0.99 (0.78; 1.25)
With correction for lead-time		
Late starters	Ref	Ref
Intermediate starters	1.13 (0.89; 1.43)	1.13 (0.83; 1.54)
Early starters	1.28 (1.01; 1.62)	1.09 (0.80; 1.47)

Notes: [a] Adjusted HR for model with mean GFR decline from PREPARE-11–3; [b] adjusted HR for the model with individual GFR declines from NECOSAD[4]. Adjusted for age, sex, ethnicity, Khan comorbidity score, primary kidney diseases, systolic and diastolic blood pressure, smoking, and antihypertensive use.
Abbreviations: GFR, glomerular filtration rate; HR, hazard ratio; CI, confidence interval; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; PREPARE-1, PREdialysis PAtient REcord-1; NECOSAD, Netherlands Cooperative on the Adequacy of Dialysis-2.

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CHAPTER 8

ESTIMATING THE OPTIMAL KIDNEY FUNCTION FOR DIALYSIS INITIATION IN PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE: USING OBSERVATIONAL DATA TO EMULATE A RANDOMIZED TRIAL

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ABSTRACT

Introduction: The optimal timing of dialysis initiation in patients with advanced chronic kidney disease is unclear. Previous observational studies compared the effect of early versus late dialysis initiation on mortality, although often limited by lead-time bias and/or immortal time bias. Furthermore, the number of patients needed to sufficiently power all comparisons at which kidney function dialysis could be initiated, renders a randomized trial unfeasible. Therefore, we performed a pilot study aiming to explore the suitability of emulating a randomized trial using observational data in an attempt to estimate the optimal kidney function at which to initiate dialysis.

Methods: Data were used from 341 patients with advanced chronic kidney disease from the observational PREPARE-2 study in order to estimate the optimal kidney function for dialysis initiation to minimize the risk of 5-year mortality. We mimicked a randomized trial in which patients would have been randomized to one of 16 treatment arms each representing a kidney function at which dialysis would have been initiated (between 5-20 ml/min/1.73m^2), after the kidney function had dropped ≤ 20 ml/min/1.73m^2 for the first time. Treatment rules were assigned based on observed treatment histories and marginal structural survival models were fitted through inverse probability weighting. Competing events of kidney transplantation were taken into account using the cumulative incidence competing risk (CICR) approach.

Results: During follow-up 154 patients started dialysis, 83 patients died of whom 48 patients died after dialysis initiation, and 34 were transplanted. Median (IQR) follow-up was 511 days (37-1854) and the median (IQR) time to dialysis initiation was 186 days (21-992). The confidence intervals for all treatment rules included the standardized CICR estimate of 1, and ranged between 0.4 and 1.6. No optimal treatment rule was observed to be associated with the lowest cumulative mortality.

Conclusion: In this pilot study we mimicked a multi-arm randomized trial, although it was too small to show any differences between different kidney function estimates at which dialysis was initiated and no clinically relevant conclusions could be drawn. Future research should be performed in larger observational studies in which also detailed information on the morbid condition of patients and time-varying kidney function and confounders are recorded.

INTRODUCTION

The optimal timing of dialysis initiation in patients with advanced chronic kidney disease is still unclear. Clinical guidelines describe that dialysis is usually started around a kidney function of 5-10 ml/min/1.73m^2.[1] Thus far, the only randomized trial that has been performed is the Initiating Dialysis Early versus Late (IDEAL) study.[2] Results were inconclusive with no clear difference in survival rates between early and late dialysis initiation.

Previous observational studies showed conflicting results, either favoring later or earlier start of dialysis, and were subjected to confounding by indication, lead-time bias and/or immortal time bias. Clinical decision-making influences the choice of a patient to start early or late with dialysis, rather than a random process. This leads to confounding by indication. Counting survival from the moment of dialysis initiation, or in other words a direct comparison between early and late starters, will introduce lead-time bias. Early starters could show a survival benefit compared to a later-starting comparative group, only due to the fact that survival time is counted from an earlier moment in time.[3] Immortal time bias is introduced in observational studies studying survival from dialysis initiation, because only people who survive long enough to actually start dialysis will be included. Aforementioned issues can be solved by conducting a randomized trial.[2] Due to randomization, confounding by indication is no issue in a randomized trial. Lead-time bias could be solved by counting survival time from a common starting point (e.g. a certain kidney function). Finally, to eliminate immortal time bias people are classified based on the treatment strategy they are assigned to prior to the start of dialysis. The issue in observational studies is often that the assigned treatment strategy per person is not recorded, only the actually received treatment. Crews *et al* and Sjölander *et al* used a similar approach as we apply in the current paper, which includes the use of treatment strategies or expanded risk sets and inverse probability weighting to address both lead-time bias and immortal time bias in comparing early, (intermediate) and late dialysis initiation.[4,5] However, these approaches did not deal with kidney transplantation as competing event for death.

To determine the optimal moment of dialysis initiation, a randomized trial with many different arms is required to include all possible starting moments based on kidney function. The number of patients needed to sufficiently power all comparisons renders this RCT unfeasible. Therefore, we aimed to perform a pilot study using the PREdialysis PAtient REcord-2 (PREPARE-2) data to emulate a randomized trial with multiple treatment arms using observational data to directly estimate the optimal kidney function level for initiating dialysis to obtain best survival, and thereby dealing with kidney transplantation as competing event.[6,7]

METHODS

Study design

The PREPARE-2 study is a prospective follow-up study of incident pre-dialysis patients of at least 18 years of age.[8,9] These patients were treated in one of 25 participating nephrology outpatient clinics in the Netherlands between July 2004 and June 2011. Patients had been referred to a specialized pre-dialysis outpatient clinic if their estimated glomerular filtration rate (eGFR) was below 20-30 ml/min/1.73m^2. At the start of specialized pre-dialysis care and in subsequent 6-month intervals, clinical data were collected. Patients with a failing kidney transplant were also included in the study if the transplantation had taken place at least 1 year ago. Patients were followed until the start of dialysis, receiving a kidney transplant, death, or censoring. The study was approved by the local Medical Ethics Committees of all participating hospitals and conducted in concordance with Good Clinical Practice Guidelines. All patients gave their written informed consent prior to study inclusion. For the present analysis, patients with at least one eGFR estimate below 20 ml/min/1.73m^2 are included.

RENINE is the Dutch registry containing patient data on chronic renal replacement therapy, defined as kidney transplant or dialysis. All Dutch dialysis centers provide data to RENINE, when patients did give their informed consent for data collection in RENINE. Data in the PREPARE-2 study were enriched with available data in RENINE, with regard to survival after initiating dialysis, because PREPARE-2 covers only the pre-dialysis period.

Exposure

The exposure is the eGFR value at which dialysis is started. This ranged from an eGFR of 5-20 ml/min/1.73m^2. The first eGFR below or equal to 20 ml/min/1.73m^2 was regarded as study entry, i.e. baseline. At baseline for each patient the possible eGFR values at which dialysis could be initiated are determined. Kidney function was estimated according to the Chronic Renal Disease Epidemiology Collaboration (CKD-EPI) formula, taking into account age, sex, race, and serum creatinine. Missing kidney function values in the observed treatment history of individuals were handled using the last observation carried forward approach. The last observed non-missing eGFR value was used to fill in missing values at a later point in the study. This was considered as the most proper reflection of clinical practice, when a patient comes to clinic and no new kidney function is available, a clinician will consider the last observed kidney function.

Outcome

Patients were followed until kidney transplantation, death prior or after the possibility of dialysis initiation and censoring. Censoring in the PREPARE-2 study is defined as restoring kidney function, emigration to another non participating center, or for this specific study when patients were followed for a maximum of 5 years after the first eGFR dropped below or was equal to 20 ml/min/1.73m^2. The outcome is defined as the standardized cumulative risk of dying (if never transplanted) within 5 years after study entry.[10] A kidney transplantation is a competing event which prevents observing death before transplantation. Once these patients receive a kidney transplant, they differ materially with regard to the outcome of interest from patients not receiving a kidney transplant.

Potential confounders

The following potential baseline confounders were considered: eGFR, all different treatment rules, age, sex, ethnicity, diastolic and systolic blood pressure, BMI, smoking status, diabetes mellitus, cardiovascular disease, primary kidney disease, serum hemoglobin, serum urea and proteinuria. Missing confounder values at study entry were imputed using the mice package in R.[11] For these variables we assumed that missing data were missing at random. All aforementioned covariates, time to dialysis initiation, follow-up time and reasons for end of follow-up (including death, transplantation or reasons for censoring) were used for imputation. A single imputed dataset was created within different bootstrap samples (see also the last paragraph in section "Weighted marginal structural survival model").

The main assumptions of marginal structural models and to emulate a trial are exchangeability, consistency, positivity and correctness of the weight-generating model.[12] Exchangeability involves the absence of unmeasured confounding. Consistency requires that the observed outcome for each participant is precisely the causal outcome under their observed treatment history.[13] Positivity requires that the probability of treatment is neither zero nor one for each combination of covariates. That is, that there are treated and untreated patients for all combinations of covariates. Treated and untreated patients were present for each treatment rule. The correctness of the weight-generating model is determined by the absence of informative censoring and no model misspecification. Exchangeability and consistency are hard to verify in any setting using observational data.[14] With regard to the assumption of exchangeability it is assumed that information for all relevant confounders is available. In that case, we mean absence of unmeasured confounding, and confounding by indication will be no issue. We performed a pilot study to explore the suitability of emulating a randomized trial

using observational data in an attempt to determine the optimal moment to initiate dialysis. In advance, it should be mentioned that the morbid condition of a patient is not objectively measured in the PREPARE-2 study, which could influence the results of this pilot study due to the presence of unmeasured confounding. In other words one could imagine that confounding by indication might stay an issue in observational studies.

Overview of analyses

To come to a recommendation about the optimal timing for initiation of dialysis in terms of survival, we considered different levels of kidney function to initiate dialysis, i.e. different treatment rules at study entry. For this purpose, different candidate treatment rules were considered as if a multi-armed trial was performed with a wide range of possible kidney functions to initiate dialysis (more details in section "treatment rules"). Study entry was defined as time zero at which we would randomize in the hypothetical RCT, in this case the first observed eGFR value equal or below 20 ml/min/1.73m^2. Based on the observed treatment history, observed eGFR values in each individual, each person was assigned to treatment rules consistent or compatible with his data. Subsequently, inverse probability weights (IPW) were used to estimate the probability of being compatible with a certain treatment rule of initiating dialysis and to adjust for non-random assignment of treatment rules (more details in section "Inverse probability weights"). Next, all possible starting moments (i.e., kidney function levels) were considered in a marginal structural survival model fitted through IPW to estimate the associated survival for each candidate treatment rule, in order to find the optimal combination of treatment rule with the lowest risk of death (more details in section "weighted marginal structural survival models"). Below follows a detailed description of the methodology used.

Statistical analyses

Data are presented as mean values with standard deviations or median with interquartile range for continuous variables, depending on the distribution, and as frequencies with percentages for categorical variables. All statistical analyses were performed using R statistical software (version 3.5.1).[15]

Treatment rules

In clinical practice, preferably more than two treatment rules than for instance early or late dialysis initiation are considered. Treatment rules are all possible eGFR values at which dialysis could be initiated. To determine the optimal treatment strategy in terms of the best expected survival, we employed the methodology as proposed by Robins *et al* and Hernan.[6,7] A similar approach was employed by Shepherd *et al.* to estimate the optimal CD4 threshold for HAART-

initiation in HIV-infected persons.[16] We mimicked their study to find the optimal kidney function for dialysis initiation in CKD patients. With this approach we are able to estimate mortality rates for each possible kidney function to directly derive the optimal kidney function at which to initiate dialysis in order to optimize survival, rather than comparing only the impact of starting dialysis in one stratum (early dialysis initiation) versus another stratum (late dialysis initiation). For example, in a previous study we corrected for lead-time bias and compared three starting groups, early, intermediate or late start of dialysis.[3] However, the current approach analyzes the data as if they came from a multi-armed randomized trial with full adherence, where a subject is assigned to one of 16 possible treatment rules corresponding to "starting dialysis within 6 months of the first eGFR measured below 20, 19, …, 5 ml/min/1.73m^2". The time window of 6 months is used because every 6 months clinical and laboratory data were assembled in the PREPARE-2 study and after each 6-month interval was determined if a patient started dialysis, ended the study, etcetera.

At study entry each person was assigned to all treatment strategies that are compatible with their observed data. In this way we emulate a multi-armed trial in which each patient is randomly assigned a value of x (=eGFR) between 5 and 20 ml/min/1.73m^2, and then asked to follow the rule "dialysis initiation within 6 months of the first eGFR measured below x". Thereby, we suppose that the multi-armed trial is analyzed by the intention-to-treat principle, thus individuals are analyzed in the treatment arm they are assigned to. Consider a patient was assigned the rule x=17. If the first eGFR of this patient below 17 was 14 ml/min/1.73m^2, and if this patient initiated dialysis within 6 months of this measurement, then this patient is adherent to his assigned rule. Of note, while this patient was randomized to the rule "dialysis initiation within 6 months of the first eGFR measured below 17", his treatment history was also compatible with the rules "dialysis initiation within 6 months of the first eGFR value measured below 16 or 15 ml/min/1.73m^2". In contrast, if this patient did not initiate dialysis within 6 months from his eGFR of 14 ml/min/1.73m^2 or if he initiated dialysis before his eGFR was estimated below 17, this patient would have been non-adherent to his assigned rule (and also non-adherent to the rules below 16 and below 15). With this model, we investigated the combination of eGFR and dialysis initiation history for each patient and determined compatible rules for each patient.

Supplementary Table S1 contains the hypothetical examples discussed below of assigning treatment histories to treatment rules. Suppose we have patient A: his first eGFR was 18 ml/min/1.73m^2, his next eGFR was 16 at month 6, and 15 at month 12. He then initiated dialysis in month 18. The data of this specific patient were compatible with the rules "initiate dialysis

within 6 months of first eGFR measured below x=16". When this patient had been assigned to the rule with x = 16, he would have been compliant because the first eGFR below (but not equal to) 16 was 15, and he initiated dialysis within 6 months after this observation. In contrast, the data of patient A are for instance not compatible with the rule "initiate dialysis within 6 months of first eGFR measured below x=17", because his first eGFR below 17 ml/min/1.73m^2 was taken more than 6 months before this patient initiated dialysis. Also, the data of patient A were not compatible with the rule "initiate dialysis within 6 months of first eGFR measured below x=15", because patient A initiated dialysis without having eGFR values below 15 ml/min/1.73m^2.

Of note, treatment rules are based on observed eGFR values rather than actual underlying GFR values. For example, patient B initiated dialysis within 6 months of his first observed eGFR (=14 ml/min/1.73m2) below for instance 20 ml/min/1.73m^2 (maximum eGFR value considered for the treatment rules). However, it could be that the actual underlying GFR dropped below 20 ml/min/1.73m^2 more than 6 months before dialysis initiation, although not observed. For the purpose of this study, we assume that the baseline eGFR is the first observed eGFR value. Patient C had a first observed eGFR of 19 ml/min/1.73m^2 and ended follow-up at month 6. This patient was compatible to all treatment rules, because the study follow-up was ended within 6 months after his first eGFR value. Therefore, it is unclear whether he was postponing dialysis initiation until a lower eGFR or preparing to start. Finally, patient D never initiated dialysis during follow-up and had two observed eGFR values of 16 and 10 ml/min/1.73m^2 at month 0 and 6. His observed data are compatible with the rule "initiate dialysis within 6 months of the first eGFR measured below x=5, …, 10", because this patient never had an observed eGFR below 10 ml/min/1.73m^2.

In some cases patients' data were not compatible to any treatment rule. For instance, patient E has an observed eGFR of 10, 12 and 11 on month 0, 6 and 12 respectively and initiates dialysis at month 18. The data of patient E were not compatible with any treatment rule as this patient initiated dialysis at month 18, but did not start dialysis within 6 months of his first measured eGFR of 10 ml/min/1.73m^2. We correct for the potential selection bias that is introduced by selecting the clones with compatible data by using inverse probability weighting (IPW), which is described below.

Assigning a person to for instance 6 treatment strategies simultaneously, as is the case for patient B, is equivalent to having 6 copies or clones of this person in the dataset, with each copy assigned to a different treatment rule. Thus, each individual contributes as many times as the number of treatment rules compatible with their data.

Inverse probability weights (IPW)

To eliminate immortal time bias, patients should be assigned to a treatment arm prior to dialysis initiation, instead of considering which treatment they actually receive. Assigning a patient to all compatible treatment rules eliminates immortal time bias, but including only compatible clones of an individual introduces potential selection bias. Patients with data compatible with a certain treatment rule may differ from patients with data compatible to other rules or not compatible to any of the treatment rules. IPW was used to account for potential bias due to non-random assignment of treatment rules.[17] Of note, this only applies under the assumption of no unmeasured confounding, confounding by indication is not solved by using IPW. IPW reweights patients in the analysis to mimic a situation in which the assignment to treatment is random. In absence of unmeasured confounding, informative censoring and model misspecification, weighting creates a pseudo-population in which the probabilities of dialysis initiation are no longer a function of the covariates but the effect of dialysis on survival is the same as in the original study population. Thus, inverse probability weighting effectively eliminates any association between prior confounders and dialysis, while preserving the association between dialysis initiation and mortality.[18]

In short, at study entry we estimated the probability of being compatible with different treatment strategies conditional on the potential baseline confounders. Therefore we used binary logistic regression. Also, quadratic and interaction terms between covariates were included in the model to obtain optimal model fit. The latter was defined as obtaining standardized mean differences ≤ 0.1 over the possible treatment rules for these covariates at baseline in the weighted dataset, in order to achieve a situation that people assigned to different treatment rules have similar prognostic factors. After fitting the logistic regression model, we checked that the standardized mean differences were ≤ 0.1 over the possible treatment rules for all covariates at baseline. For each compatible treatment rule per individual, the predicted probability was computed of being compatible with the assigned treatment strategy. Inverse probability weights were obtained by taking the inverse of these predicted probabilities. People who are not compatible, transfer their weight in the analysis to those who have compatible data.[7] In case inverse probability weights had a value higher than 10, they were truncated, to avoid that extreme observations would disproportionately impact the results. After assigning inverse probability weights to the clones, clones without compatible rules were omitted from further analysis.

Weighted marginal structural survival model

After assigning individuals to all compatible treatment rules compatible with their data to avoid immortal time bias and assign IPW to correct for selection bias introduced by this step, a marginal structural survival model was fitted through IPW to estimate the separate effects on cumulative risk of death of starting dialysis at different levels of kidney function. It is a marginal model, because it is not conditional on confounders and structural because we handled counterfactual outcomes by using IPW.[19]

In these obtained weighted data (weighted using inverse-probability weights) a cumulative incidence competing risk (CICR) approach was used to obtain cumulative risk of death for each possible eGFR to initiate dialysis.[10] Instead of computing a single cumulative mortality, this approach computes the cumulative mortality for each treatment rule and this yields the treatment rule with the lowest cumulative mortality. The obtained cumulative mortality is not meant for prognostic purposes, but purely for comparison of treatment rules. Therefore, we standardized the obtained CICR estimates by dividing the cumulative risk of deaths by the mean mortality rate in the original population. The mean mortality rate is calculated as overall CICR estimate. In this way, we aimed to find the eGFR rule for initiating dialysis that relates to optimal survival, or the lowest cumulative risk of death after 5 years. The 95% confidence intervals for each treatment rule were constructed based on the 2.5th and 97.5th percentiles of the distribution of the estimated effects of the eGFR rules in each of 1000 bootstrap samples.[16] Bootstrapping was performed prior to cloning and imputation, therefore no multiple imputation was performed.[20]

Sensitivity analyses

To test the robustness of the results, three sensitivity analyses were performed. Firstly, instead of treatment rules of every kidney function, categories were made of the rules "initiate dialysis within 6 months of the first eGFR measured below 20, below 16, below 12, or below 8". This is mainly done from a clinical point of view, considering the general variability in kidney function over time and the uncertainty around estimating the GFR based on the CKD-EPI equation. Secondly, the summary illness perception score at baseline was taken into account as covariate in the binary logistic regression model for confounding adjustment. Thirdly, to visualize the asymptotic theory and assess the impact on the effect estimates, the original sample was quadrupled in a simulation.[21]

RESULTS

Of 502 patients included in the PREPARE-2 study, 341 patients had a treatment history compatible with any of the treatment rules and 28 patients were excluded because their observed eGFR values never dropped to or below 20 ml/min/1.73m^2. 133 patients were excluded whose data was not compatible with any treatment rule, as for instance patient E in Supplementary Table S1. For included patients, baseline characteristics are shown in Table 1. Baseline characteristics of excluded patients are shown in Supplementary Table S2. The baseline characteristics of included and excluded patients were comparable. Also, cumulative risk of 5-year mortality was similar (24% versus 25% in included and excluded patients). Of the 341 included patients, 67% was male, 94% was Caucasian, and renal vascular disease was the most common primary kidney disease. At study entry, the median (IQR) age was 66.8 (53.1-76.4), and the median value of the first eGFR was 14.0 (10.9-18.1) ml/min/1.73m^2. Median (IQR) follow-up was 511 days (37-1854).

During follow-up 154 patients started dialysis, the median (IQR) time to initiation was 186 days (21-992). Furthermore, in total 83 patients died of which 48 patients died after dialysis initiation, and 34 received a kidney transplant during follow-up. Table 2 contains the number of patients who had an event within each 6-month interval, up to 60 months after study entry.

Emulating a randomized trial to avoid lead-time bias and immortal time bias yielded the results as shown in Figure 1. Overall 5-year cumulative risk of death before transplantation was 21.9%. Figure 1 demonstrates the CICR estimates belonging to each eGFR treatment rule to initiate dialysis to minimize the 5-year standardized cumulative risk of death. No optimal treatment rule was observed to initiate dialysis.

Using 4 instead of 16 treatment rules yielded 310 patients that were compatible with any of the treatment rules. Results are shown in Figure 2 and were similar to those in Figure 1. Including the baseline summary illness perception scores in the binary logistic regression model to calculate IPW yielded similar results as those shown in Figure 1 (data not shown). As expected, quadrupling the sample size generated twice as small confidence intervals and effect estimates were hardly influenced by this (Supplementary figure S1). For instance, a relative difference of 25% compared to the overall cumulative risk of death seems to be a relevant difference when comparing dialysis initiation with the first eGFR below 7 versus higher than 10 ml/min/1.73m^2.

Table 1. Baseline characteristics

	Individuals with compatible rules based on observed treatment history, n=341 [a]
Sex, male	230 (67.4)
Age, years	66.8 (53.1-76.4)
Ethnicity	
Caucasian	319 (93.5)
Asian	2 (0.6)
Black	17 (5.0)
Other	3 (0.9)
Primary Kidney Disease	
Diabetes Mellitus	49 (14.4)
Glomerulonephritis	49 (14.4)
Renal vascular disease	100 (29.3)
Other	143 (41.9)
Smoking status	72 (21.2)
Systolic blood pressure	142.1 (±22.0)
Diastolic blood pressure	78.1 (±11.7)
Diabetes Mellitus, yes	86 (25.2)
Cardiovascular Disease, yes	204 (59.8)
Body Mass Index, kg/m²	26.7 (±4.9)
eGFR baseline, ml/min/1.73m²	14.0 (10.9-18.1)
Serum urea	22.9 (±7.3)
Hemoglobin, mmol/L	7.6 (±0.9)
Proteinuria, g/24h	0.6 (0.3-1.2)

Values are given as frequency (percentage), mean (±SD) or median (IQR), as appropriate.
[a] Missings: 0.9% (n=3) systolic and diastolic blood pressure , 1.2% (n=4) Body Mass Index, 0.3% (n=1) diabetes, 0.3% (n=1) smoking status, 5.9% (n=20) serum hemoglobin, 10.6% (n=36) serum urea, 61.3% (n=209) 24 hour albuminuria at baseline.

Table 2. Number of patients who initiated dialysis, who died, or received a kidney transplantation

Months of follow-up	No. dialysis initiation	Total No. deaths	No. death after dialysis initiation	No. kidney transplantation
6	79	12	0	3
12	33	13	6	11
18	18	13	4	9
24	11	9	7	4
30	7	8	6	2
36	4	6	5	3
42	2	9	6	2
48	0	9	10	0
54	0	2	2	0
60	0	2	2	0
Total	**154**	**83**	**48**	**34**

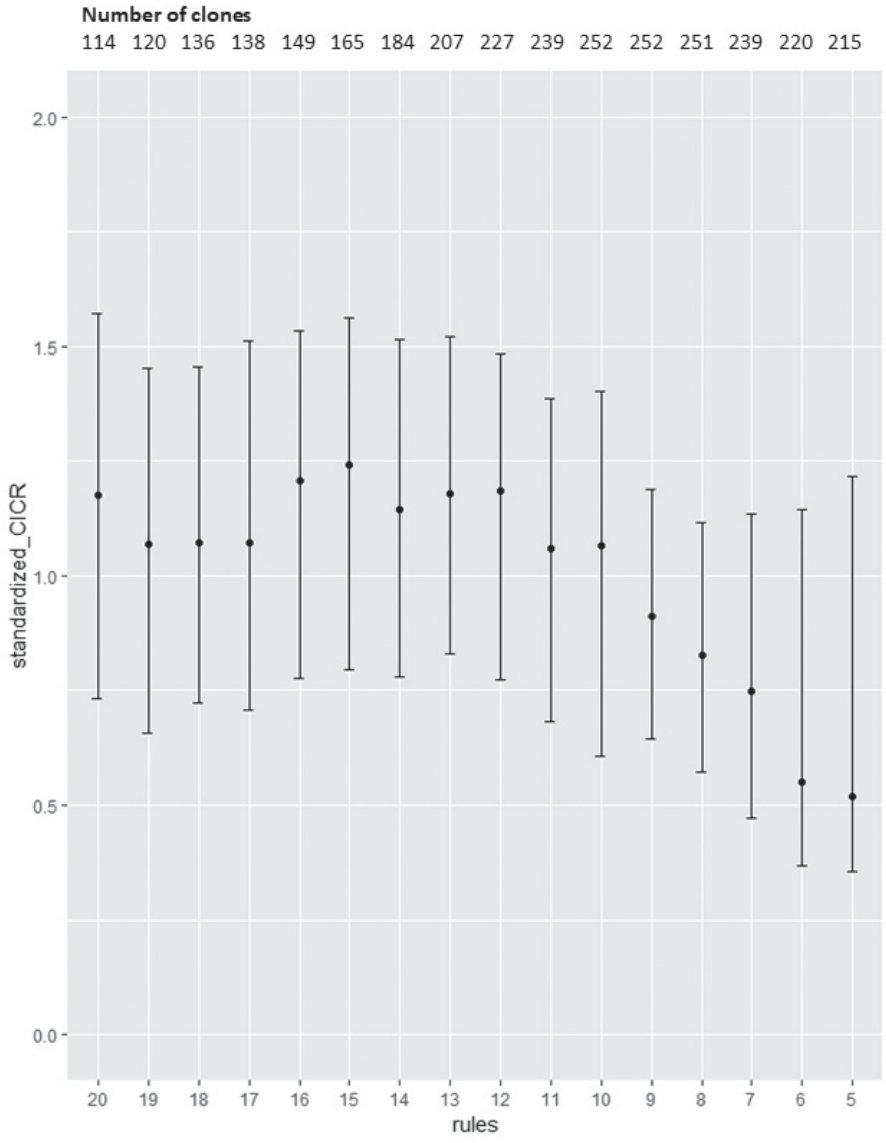

Figure 1. The standardized CICR estimates for each treatment rule, which presents the cumulative risk of death achieved for the associated eGFR rule (for dialysis initiation) compared to the overall mortality in the original study population after 5 years of follow-up. Number of clones with compatible data is shown at the top of the figure.
Abbreviation: CICR = cumulative incidence competing risk.

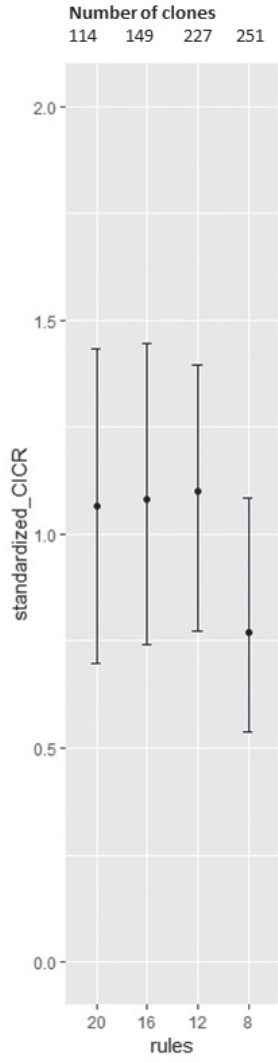

Figure 2. The standardized CICR estimates for 4 treatment rules (<20, <16, <12, <8; instead of the original 16 treatment rules), which presents the cumulative risk of death achieved for the associated eGFR rule (for dialysis initiation) compared to the overall mortality in the original study population after 5 years of follow-up. Number of clones with compatible data is shown at the top of the figure.
Abbreviation: CICR = cumulative incidence competing risk.

DISCUSSION

In this pilot study, we demonstrated the emulation of a multi-armed randomized trial using observational data in an attempt to estimate the optimal eGFR level for initiating dialysis in terms of the lowest standardized cumulative 5-year mortality risk. Although this method seems promising to answer the proposed research question, our dataset was too small to show any differences between different eGFRs at which dialysis was initiated and no clinically relevant conclusions could be drawn.

To the best of our knowledge this is the first study emulating a multi-armed randomized trial using observational data in an attempt to find an optimal kidney function for dialysis initiation. Previously, only one randomized trial, the IDEAL study, has been performed, in which early and late starters were compared and no survival benefit was observed for one of the two starting groups.[2] Several observational studies have been performed, which showed contradictory results whether early or late dialysis initiation is preferred to obtain the lowest mortality.[22] Additionally, observational studies are often subjected to confounding by indication, lead-time bias and/or immortal time bias. For instance, in a previous study, we were able to correct for lead-time bias and showed that this is not only a methodological problem but also has clinical impact.[3] However, immortal time bias was still an issue here. Only people who survived long enough to initiate dialysis were included. Sjölander *et al* and Crews *et al* used a similar statistical approach as we used in the current paper, which they also called treatment strategies or the use of expanded risk sets and inverse probability weighting to address both lead-time bias and immortal time bias in comparing different strategies for dialysis initiation.[4,5] However, both approaches did not deal with the competing events of kidney transplantation. Furthermore, these previous studies often compared only a few categories of kidney function at which dialysis was initiated, instead of using multiple treatment arms. The latter is necessary to consider an optimal kidney function to start not too early and not to withheld therapy for too long.

A main advantage of emulating a randomized trial is that multiple treatment rules could be considered, rather than only the early or late start of dialysis, in a setting where lead-time bias and immortal time bias are handled. By using the CICR approach we were able to handle competing events of kidney transplantation. Furthermore, the rule "initiate dialysis within 6 months of the first eGFR measured below value x" reflects clinical practice in that 6 months is a typical length of time between visits in nephrology clinic. Nevertheless, we were unable to find an optimal eGFR for dialysis initiation associated with the lowest mortality. 95% confidence

intervals obtained for the standardized CICR estimates for each treatment rule showed a large uncertainty. Preferably, we would also have estimated the 95%-confidence interval around the optimal treatment rule, although in this case infeasible due to imprecise CICR estimates. The current study showed that the used modelling techniques are data hungry and more data is required than we had at our disposal. The results of our sensitivity analysis to quantify the data hungriness, indicate that future studies using observational data to emulate a randomized trial should include at least 1500 patients with more than 300 death events. Our treatment rules for dialysis initiation were defined based on kidney function alone. To reflect clinical decision-making, also other factors as symptom presence and severity should be involved in the treatment rule.[23] Also, possible unmeasured confounding could be present due to the lack of detailed assessment of symptoms and clinicians might have influenced the moment of dialysis initiation as observed in the PREPARE-2 study. Thus, more time-varying information on symptoms and patient performance is needed to meet the assumption of no unmeasured confounding. After performing this pilot study we are a step closer to how we can find the optimal moment for dialysis initiation, by eliminating issues as lead-time bias and immortal time bias involved in analyzing observational data. The European QUALity study on treatment in advance chronic kidney disease (EQUAL study) is an ongoing prospective cohort study in elderly patients, and might be the appropriate setting to ultimately answer this question.[24]

Considering aforementioned results of our pilot study, we would like to provide recommendations for future research. Effect estimates did not change considerably when quadrupling the sample, but confidence intervals became twice as small, as expected. Therefore, we recommend the use of larger datasets with at least 1500 patients with advanced chronic kidney disease and at least 300 deaths. This considers large prospective cohort studies with long follow-up or possibly registry-based cohorts would contain sufficient events to overcome the power issue. Another requirement would be more detailed information on the morbid condition of patients, including evaluation of symptom number and severity to ensure that the assumption of no unmeasured confounding applies.[25] One has to keep in mind that defining the treatment rules according to both symptom development and kidney function requires an even larger sample size. Instead of restricting data to 6-month intervals, a time granularity based data structure could be considered. With a time granularity based data structure we mean that all available kidney function values and time-varying confounders are included to perform time-varying instead of constant marginal structural survival analyses. One side note, the treatment rules are still based on estimated kidney functions and not the actual underlying kidney function values. However, the additional benefit is that the impact of possible measurement error or

variability in kidney function values will be less extreme when all measurements are taken into account. Furthermore, one might consider using interpolated kidney function trajectories instead of observed kidney functions to obtain less varying and more stable patterns of kidney functions over time, as previously used by Sjölander *et al* and Crews *et al*.[4,5] Finally, one has to keep in mind that in the current pilot study informative censoring could be present due to patient censoring when kidney function was restored. However, this only applied to 5% of the original patient sample. This type of information is important to keep in mind for the assumption of no informative censoring. The big question remains: Should we try to perform a randomized trial after all? In our opinion, this is still not feasible to find an optimal starting moment for dialysis considering the sample size and detailed information needed, besides the associated long follow-up period to reach enough events. However, if at least aforementioned information is available in large observational data and the proposed analyses for emulating a randomized trial could be performed properly, this yields an optimal treatment rule for dialysis initiation. Then a two-arm randomized trial could be performed to assess the impact of usual care versus the obtained optimal treatment rule to initiate dialysis.

In conclusion, we performed a pilot study in which we emulated a randomized trial using observational data in an attempt to estimate the optimal kidney function for dialysis initiation in terms of survival, thereby avoiding lead-time bias and immortal time bias. We provided several recommendations for future research, including the use of larger and more detailed data sources on disease symptoms, which might be possible in the EQUAL study.

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SUPPLEMENTARY MATERIAL

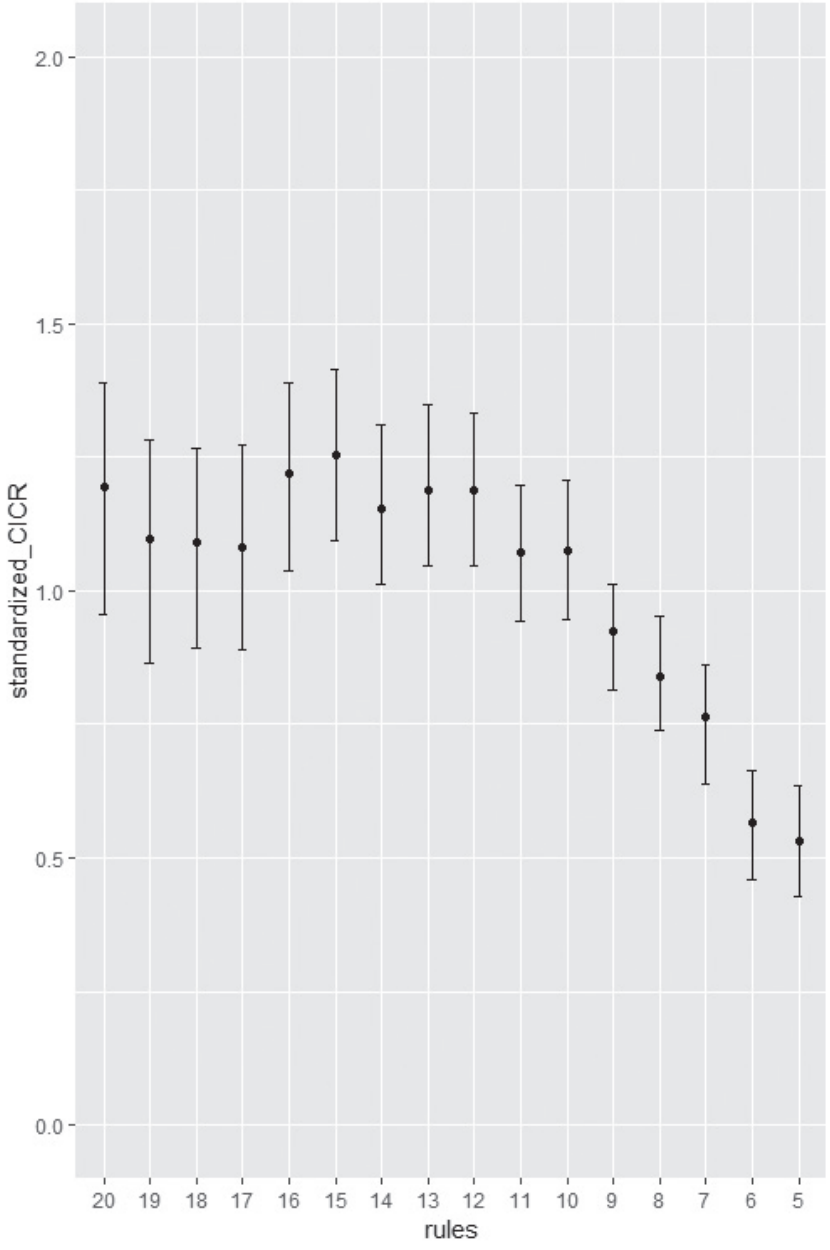
Table S1. Hypothetical examples of assigning treatment rules compatible with patients' treatment history

Patient	Month after study entry				Compatible treatment rules
	0	6	12	18	"Start dialysis within 6 months of first eGFR value measured below x"
A	18	16	15	Dialysis	x=16
B	14	Dialysis			x=15,…,20
C	19	Study end			x=5,…,20
D	16	10	Study end		x=5,…,10
E	10	12	11	Dialysis	Not compatible with any x

Table S2. Baseline characteristics of excluded individuals

	Individuals without compatible rules based on observed treatment history, n=161 [a]
Sex, male	111 (68.9)
Age, years	70.2 (60.2-75.5)
Ethnicity	
Caucasian	143 (88.8)
Asian	3 (1.9)
Black	12 (7.8)
Other	3 (1.9)
Primary Kidney Disease	
Diabetes Mellitus	23 (14.3)
Glomerulonephritis	18 (11.2)
Renal vascular disease	54 (33.5)
Other	66 (41.0)
Smoking status	27 (16.8)
Systolic blood pressure	143.1 (±22.5)
Diastolic blood pressure	77.4 (±11.4)
Diabetes Mellitus, yes	42 (26.1)
Cardiovascular Disease, yes	91 (56.5)
Body Mass Index, kg/m²	26.9 (±5.7)
eGFR baseline, ml/min/1.73m²	15.1 (11.5-21.2)
Serum urea	23.0 (±6.3)
Hemoglobin, mmol/L	7.7 (±0.9)
Proteinuria, g/24h	0.5 (0.2-1.1)

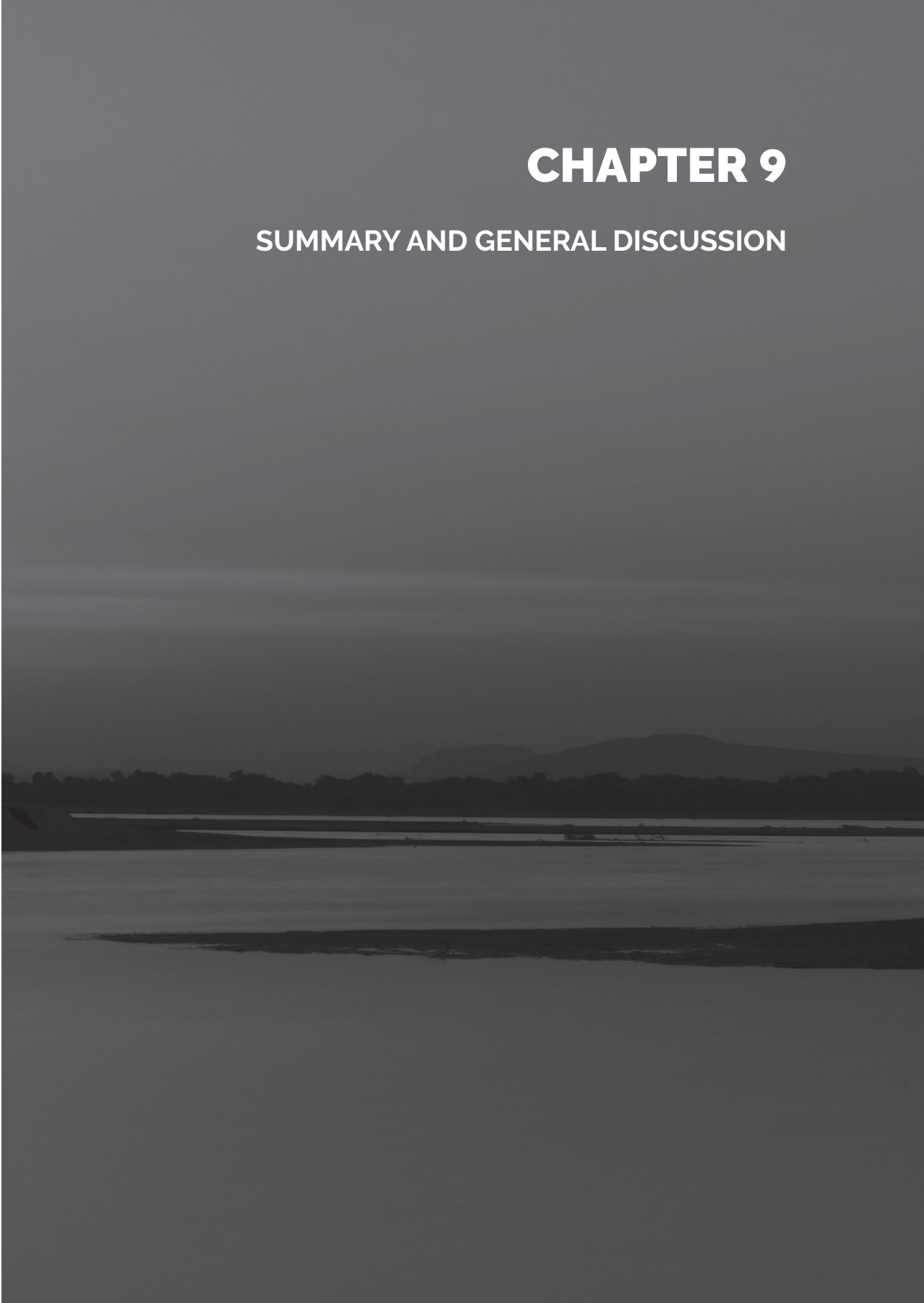
Values are given as frequency (percentage), mean (±SD) or median (IQR), as appropriate. a Missings: 24.2% (n=39) baseline eGFR, 0.6% (n=1) systolic and diastolic blood pressure, 3.7% (n=6) Body Mass Index, 24.8% (n=40) serum hemoglobin, 26.1% (n=42) serum urea, 59.0% (n=95) 24 hour albuminuria at baseline.



Supplementary figure S1. The standardized CICR estimates for each treatment rule in the quadrupled sample size, which presents the cumulative risk of death achieved for the associated eGFR rule (for dialysis initiation) compared to the overall mortality in the original study population after 5 years of follow-up.
Abbreviation: CICR = cumulative incidence competing risk.

CHAPTER 9

SUMMARY AND GENERAL DISCUSSION



In this thesis, we provided insight into clinical and methodological issues involved in studying when to start dialysis in terms of survival in patients with moderate to advanced CKD. For this purpose we focused on methodological issues, such as in which type of cohort and patients CKD progression should be studied and what the best method is for analyzing kidney function trajectories. Subsequently, we studied clinical issues like kidney function trajectories and risk factors for CKD progression important for guiding clinical decision-making and anticipating treatment choices. For finding an optimal moment for dialysis initiation, we highlighted the importance of taking account of lead-time bias and immortal time bias and we showed options how to deal with these issues. In this chapter a summary is presented of our main observations, strengths and limitations of our research are discussed and implications are provided, including recommendations for future research.

Summary of main observations

Knowledge about the rate of CKD progression prior to the start of RRT is important for clinical decision-making and anticipating treatment choices and priorities. In **chapter 2** we showed in a systematic review and meta-analysis that substantial heterogeneity exists in reported kidney function decline in patients with advanced CKD not on dialysis. To our knowledge, we have been the first to make a clear distinction between studying kidney function decline in CKD cohorts and in dialysis-based studies. In the latter, patients are selected based on the fact they started dialysis, possibly leading to an overestimation of the true underlying kidney function decline prior to dialysis initiation. We included 60 studies (43 CKD cohorts, 17 dialysis-based studies) and found a substantial difference in weighted annual mean [95%-confidence interval (95%-CI)] kidney function decline for these two study designs: 2.4 (2.2, 2.6) mL/min/1.73m^2 in CKD cohorts versus 8.5 (6.8, 10.1) mL/min/1.73m^2 in dialysis-based studies [difference 6.0 (4.8, 7.2)]. Importantly, due to biased estimates in studies that included solely patients that progressed towards dialysis, data on CKD progression from studies that prospectively followed CKD patients should be used to guide clinical decision-making in non-dialysis patients.

Besides the type of study design, the selection of prevalent or incident patients also impacts the validity of a risk factor study. In **chapter 3** we discussed the potential differences in effect estimates for a range of clinical risk factors in association to all-cause mortality when comparing a prevalent to an incident dialysis population. We found that effect estimates may differ substantially, most often resulting in weaker effects in prevalent than incident patients, but varying to stronger effects and even opposite effects. In line, we showed differences in the risk factor prevalence in prevalent and incident patients that could be considerable. These differences between incident and prevalent cohorts may be explained by selection bias. In a

prevalent dialysis cohort, patients must have survived a certain amount of time in order to be included in the cohort. Patients dying early in the dialysis course will have more mortality-related risk factors than patients who survived until sampling in the prevalent cohort, and the patients included in the prevalent cohort are not a random sample of all patients in the incident cohort. Now, when studying a risk factor-outcome association, patients with the risk factor under study included in a prevalent cohort have survived until sampling, and are thus less likely to have other risk factors for mortality. As prevalent patients with the studied risk factor are by design less likely to have other risk factors for mortality than prevalent patients without the studied risk factor, there is a problem of incomparability and the risk estimation from such a comparison is likely biased. This is the problem of selection bias. Importantly, the fact that the selection of patients is associated with the risk factor under study in itself does not necessarily bias the estimates of the risk factor-outcome association. Selection bias will arise when other factors are involved that determine patient selection and are also a risk factor for the outcome (irrespective of their relation to the studied risk factor). When all such factors are measured appropriately and adjusted for, selection bias could be solved. However, in general this is unlikely; therefore we would argue for the use of incident cohorts when studying these risk factor-outcome associations.

In addition to choosing the appropriate study design and participants to be included, CKD progression has to be studied properly. In **chapter 4** we aimed to create awareness about the distinction between using linear mixed-effects models (LMMs) and linear regression analysis on individual slopes. With the clinical example of the effect of baseline diastolic blood pressure on kidney function decline we showed that these two approaches yielded different results. Effect estimates differed approximately twenty percent. We showed that LMMs are the preferred and recommended model for research questions regarding kidney function trajectories over time at population level. Typically, the kidney function of included patients is estimated at several time points. During follow-up, some patients may drop out earlier than others and for different reasons. This heterogeneity with respect to dropout and number of kidney function estimates between individuals are accurately handled by LMMs. Missing values of kidney function are handled properly in LMMs when they are related to previously observed eGFR values, because the LMM estimates the individual slope also based on complete observed data of other similar individuals in the dataset. Missing values in other covariates are not handled by the LMM. Finally, individual differences in both baseline kidney function and slopes of kidney function decline are taken into account by the fixed and random effects in LMMs.

After gaining more insight into the way we should obtain and analyze data on CKD progression appropriately, we focused on the association between kidney function decline and the symptom development in non-dialysis dependent patients with advanced CKD of ≥65 years and a kidney function that dropped below 20 mL/min/1.73m^2 (**chapter 5)**. These patients were followed in the EQUAL study for one year. LMMs were used to assess the association between kidney function decline and symptom development. Previous studies were limited by their cross-sectional design and showed no association between kidney function and symptoms. To our knowledge, we are the first that have shown in more than a thousand patients that a faster kidney function decline was associated with a steeper increase in both symptom number and severity. Our results seem to suggest the need for repeated thorough assessment of symptom development during outpatient clinic visits, in addition to the monitoring of kidney function decline, for anticipating the need for dialysis initiation.

In **chapter 6** we focused on studying the effect of serum calcium on CKD progression for separate CKD stages. More specifically, we studied the association between baseline serum calcium and the subsequent rate of kidney function decline in separate CKD stages 3a, 3b, 4 and 5. Therefore, we used LMMs in a CKD 3-5 cohort of 15755 adult citizens of Stockholm, for whom creatinine tests taken during 2006-2011 and concurrent calcium testing was available at cohort entry. Our results showed that in the advanced CKD stages 3b to 5, higher baseline serum calcium was associated with less rapid kidney function decline. Thereby, lower serum corrected calcium seemed to be indicative for vitamin D deficiency. However, in CKD stage 3a no association was observed between baseline serum calcium and the subsequent rate of kidney function decline. This paper illustrated that studying CKD progression in separate CKD stages could be very informative, because effect estimates differ among stages of disease.

Knowledge of CKD progression in a broader sense is important to anticipate when or not to initiate dialysis. However, there are more issues to keep in mind for finding the optimal moment to initiate dialysis when relying on observational study data. In **chapter 7** our results confirmed that lead-time bias is not only a methodological problem, but has also clinical impact when investigating the optimal kidney function for dialysis initiation in terms of survival. 1143 patients with eGFR data at dialysis initiation, including 852 patients with mGFR data, were included from the NECOSAD cohort. The effect of lead-time bias was assessed using Cox proportional hazards models, and survival was either counted from the time of dialysis initiation or from a common starting point (GFR=20 mL/min/1.73m^2). We estimated the common starting point to correct for lead-time bias in two ways, using an average annual kidney function decline and using individual decline rates prior to dialysis initiation, therefore two HRs were obtained for

lead-time corrected results. Without lead-time correction, no difference between early and late starters was present based on the estimated glomerular filtration rate (GFR) (HR 1.03 [95% confidence interval: 0.81-1.30]). However, after correction for lead-time bias, early initiation showed a survival disadvantage (HR between 1.10 [0.82-1.48] and 1.33 [1.05-1.68]). Based on measured GFR, the potential survival benefit for early starters without lead-time correction (HR 0.80 [0.62-1.03]) completely disappeared after lead-time correction (HR between 0.94 [0.65-1.34] and 1.21 [0.95-1.56]). Our results indicated that early dialysis initiation, based on the definition of kidney function alone, was not associated with an improvement in survival. Of note, lead-time bias was solved here, although immortal time bias and confounding by indication were still an issue.

Therefore, we performed a pilot study to investigate the suitability of emulating a randomized trial using observational study data to deal with both lead-time bias and immortal time bias in **chapter 8.** Data of 341 patients with advanced CKD were used from the observational PREPARE-2 study in an attempt to estimate the optimal kidney function for dialysis initiation. We emulated a randomized trial in which patients would have been randomized to one of 16 treatment arms at baseline, each treatment arm representing a kidney function value between 5-20 ml/min/1.73 m^2 at which dialysis could be initiated. We mimicked a randomized trial in which an intention to treat analysis was applied. Marginal structural survival models with a cumulative incidence competing risk approach were fitted through inverse probability weights. By using inverse probability weights we aimed to correct for the non-random assignment of the treatment rules. During follow-up 154 patients started dialysis, 34 were transplanted and 83 patients died of whom 48 patients died after dialysis initiation. No optimal treatment rule was observed to be associated with the lowest cumulative mortality, due to large uncertainty around effect estimates (reflected by wide confidence intervals). This pilot study appeared to be too small to show any differences between different kidney function estimates at which dialysis was initiated and therefore no clinically relevant conclusions could be drawn. Our results indicate that analyses should be performed in larger observational studies in which also detailed information on the morbid condition of patients, and time-varying kidney function and confounders are recorded.

Bigger picture from CKD progression to dialysis initiation

Following current research guidelines for patients with CKD, timely referral to specialist kidney care is recommended, that is when a patient reaches a GFR below 30 ml/min/1.73 m^2, or CKD stage 4.[1] This pre-dialysis care aims to slow down kidney disease progression and to prepare patients for their potential start of RRT. These guidelines also state that progressive CKD

should be managed in a multidisciplinary care setting, including education and counseling on different RRT modalities, dietary advice, and psychological and social care.[1] Detailed knowledge on the rate of kidney function decline in patients with moderate to advanced CKD prior to the start of RRT could guide clinical decision-making and anticipate treatment choices and priorities.[2-4] With our meta-analysis, we showed that patients with moderate to advanced CKD have a weighted mean annual kidney function of 2.4 (2.2, 2.6) mL/min/1.73m^2. In addition, we underlined the importance of studying CKD progression in an incident cohort in which patients are identified at a well-defined point in the course of kidney disease progression. Also, we showed the importance of analyzing CKD progression using LMMs that accurately handle dropouts, heterogeneity in number of kidney function estimates between individuals and individual differences in both baseline kidney function and slopes of kidney function decline. We stressed that these methodological issues lead to different results and are extremely important to take into account before applying results in a clinical setting.

CKD progression could, besides conservative management, ultimately lead to the need for RRT or dialysis initiation. The KDIGO guideline for decision-making on timing of dialysis initiation states that dialysis should be initiated based on uremic signs and symptoms, often in the eGFR range between 5 and 10 mL/min/1.73m^2.[5] However, there is a wide variety in starting moments in patients with advanced CKD. The only randomized trial performed on when to start dialysis is the Initiating Dialysis Early And Late (IDEAL) study.[6] Patients were randomized to an early versus late start dialysis based upon estimated GFR (eGFR). In this study physical symptoms played an important role in deciding if and when to initiate dialysis. A large proportion of patients randomized in the late starting group initiated earlier due to the presence of uremic symptoms. However, the relationship between kidney function and symptoms has so far only been studied in a cross-sectional setting or between categories of symptoms and kidney function decline (stable, improved or worsening).[7-9] To date, no association was found between kidney function and symptoms. In this thesis, we confirmed the absence of a cross-sectional association between kidney function level and symptoms. However, we elaborated the evidence by showing that a faster kidney function decline associates with a more progressive increase in both the number and the severity of symptoms in incident patients who dropped below 20 ml/min/1.73m^2 for the first time. This suggests the need for repeated thorough assessment of symptom development during outpatient clinic visits, for instance with patient reported outcome measures (PROMs), in addition to the monitoring of kidney function decline, for clinical decision-making in preparation for the possible start of RRT. Current research such as the SWIFT (symptom monitoring with feedback trial) in Australia/New Zealand and

OPT-ePRO (OPTimising routine collection of electronic Patient-Reported Outcomes into disease registries) in the UK are investigating the effectiveness of routinely capturing PROMs in renal care. Ultimately, a clinical decision rule, including kidney function decline and symptom development, may be useful to decide when to start dialysis. Of course, we have to keep in mind that nonspecific symptoms could be related to other comorbid conditions or illnesses precipitating early dialysis initiation among some providers.

Returning to the question on when to start dialysis, in the only trial performed so far, the IDEAL study, no difference was observed in the survival between the early and late starting groups. Our expectation is that starting too early would be harmful whereas on the other hand, waiting too long would also be harmful. To determine the optimal moment of dialysis initiation, a randomized trial with many different arms would be required to include all possible starting moments. Preferably the starting moment would be defined based on a combination of kidney function and symptom burden. The number of patients needed to sufficiently power all comparisons renders this randomized trial unfeasible. It is unlikely that long-term trials will ever be conducted to compare each of the possible starting moments. Hence, appropriate analysis of observational data is our best chance to estimate the timing of dialysis initiation.

Several observational studies have investigated when to start dialysis in terms of kidney function and showed contradictory results. Some studies suggested better survival for patients who started dialysis early (i.e. high kidney function), whereas most studies suggested better survival for those who started late (i.e. low kidney function).[10-26] However, when studying the starting moment of dialysis in an observational cohort setting, several issues have to be kept in mind. This concerns lead-time bias and immortal time bias. Step by step we tried to solve these issues in an observational study setting. Of these aforementioned studies, only four have taken account of lead-time bias, but none were based on both estimated GFR and measured GFR and all had small study populations.[12, 13, 17, 25] We showed that lead-time bias is not only a methodological problem, but also has clinical impact when studying the timing of dialysis initiation. Observations in this thesis showed that the survival benefit for early starters completely disappeared when early starting was defined based on measured GFR. In that analysis immortal time bias was still an issue, although the influence of this bias was considered minimal because a low percentage dropped out due to death in the study. Immortal time bias and lead-time bias could be solved by emulating a randomized trial using observational data as we showed in our pilot study. Previously, Sjölander *et al* used a similar statistical approach based on expanded risk sets and inverse probability weighting to address both lead-time bias and immortal time bias in comparing different strategies for dialysis initiation.[27] The results

obtained, using this method, suggested roughly equal survival curves for early and intermediate starters and better survival for late starters, although not significant. However, this approach did not deal with the competing events of kidney transplantation and only three treatment arms were considered.

Methodological strengths and limitations for finding the optimal moment for dialysis initiation

The main strength of this thesis is the variety of methodological issues discussed that showed to have clinical impact on the reported CKD progression and when to start dialysis. Furthermore, for this purpose we used a broad range of study cohorts. These include NECOSAD, PREPARE-1, PREPARE-2, SCREAM and the EQUAL study.

Though this thesis has brought us closer to a methodologically sound approach for finding the optimal moment to initiate dialysis in terms of survival, two main issues remain to be solved. First, emulating a randomized trial requires a lot of detailed information to provide enough power to include all treatment strategies in the model. Therefore large observational databases are needed both in terms of assembled information and in number of patients, visits and events. Registries often not include the needed detailed information and cohort studies are often limited by their number of events. Second, to emulate a randomized trial there are several assumptions that need to be met. One of the assumptions is the absence of unmeasured confounding. In a real randomized trial patients are randomized across treatment arms and based on randomization it is assumed that patients in different treatment arms would have a similar prognosis. In observational studies clinical decision-making or the indication on when to start dialysis could be influenced by doctors' preference, patients' condition, general appearance of a patient, symptom burden etcetera. As in observational studies often not all this information is available, it is important to consider if enough information is available to assume that confounding by indication does not bias the results. Unfortunately, we did not have enough data at our disposal to correct for confounding by indication, which probably has influenced our results. The general, almost philosophical question remains if we could ever reliably assume the absence of confounding by indication or unmeasured confounding when studying the optimal moment of starting dialysis.

To emulate the random assignment, proper adjustment for all confounders is required to ensure exchangeability, for instance via inverse probability weighting. Inverse probability weighting is used in this thesis under the assumption of no unmeasured confounding. However, as we mentioned earlier this pilot study may have been limited by confounding by

indication hampering proper adjustment for non-random assignment. In general it is impossible to determine whether the emulation of a trial failed due to the presence of unmeasured confounding. However, Hernan and Robins propose indirect approaches that may alert a researcher about possible presence of unmeasured confounding, which could be considered in future research.[28] One approach is to consider negative controls for the outcome for which we do not expect a causal effect.[29] If the confounders for the study and control outcomes are sufficiently comparable, then the use of control outcomes might help to detect confounding. Another option is to consider control outcomes for which the effect size is known and is not equal to zero. Or treatment controls could be considered with treatment strategies with indications similar to the treatment strategies under study, but for which no effect is expected. A different approach is to consider extracting information from sources previously considered impractical for large-scale research. This could be, for instance, advanced image processing and novel technologies for natural language processing which might capture a patients' condition.[28]

Implications and recommendations for future research

In this thesis we showed the clinical impact of several methodological issues that should be taken into account when studying CKD progression and in order to find an answer to the question when to start dialysis.

From a methodological point of view, we have several recommendations for future research. We recommend studying associations of risk factors with CKD progression in an inception cohort, with incident patients using LMMs and stratification on disease stages to provide further insight into the presence or absence of the association of interest during disease progression.

Besides studying CKD progression, which could eventually lead to the need for RRT or dialysis initiation, we have to keep in mind two main issues when analysing data from observational studies to find the optimal moment for dialysis initiation are lead-time bias and immortal time bias. Since we rely on observational study data, we showed in a pilot study how observational data could be used to emulate a randomized trial to deal with both lead-time bias and immortal time bias. Our pilot study, using the PREPARE-2 data, appeared to be too small to show any differences between different kidney function estimates at which dialysis was initiated and no clinically relevant conclusions could be drawn. In our opinion, a true randomized trial is not feasible considering the sample size and detailed information needed, besides the associated long follow-up period to reach enough events. Furthermore, we should keep in mind the issue of confounding by indication as discussed previously. For future research on studying the optimal moment for dialysis initiation, we would recommend performing analyses in larger

observational studies with long follow-up and the data has to contain sufficient events to overcome the power issue, including at least 1500 patients with advanced chronic kidney disease and at least 300 deaths. We recommend that also detailed information on the morbid condition of patients is available, including evaluation of symptom number and severity to ensure that the assumption of no unmeasured confounding applies.[30] For future research it is important to realize that defining treatment rules according to both symptom burden and kidney function may require an even larger sample size. We recommend using a data structure that allows different time domains, so that all available kidney function values and time-varying confounders are included to perform time-varying instead of constant marginal structural survival analyses. The additional benefit is that the impact of possible measurement error or variability in kidney function values will be less extreme when all measurements are taken into account.

The question when to start dialysis is important and to a large extent still unsettled. We believe that the methodology and recommendations provided above will be highly useful to find a more definitive answer in future research.

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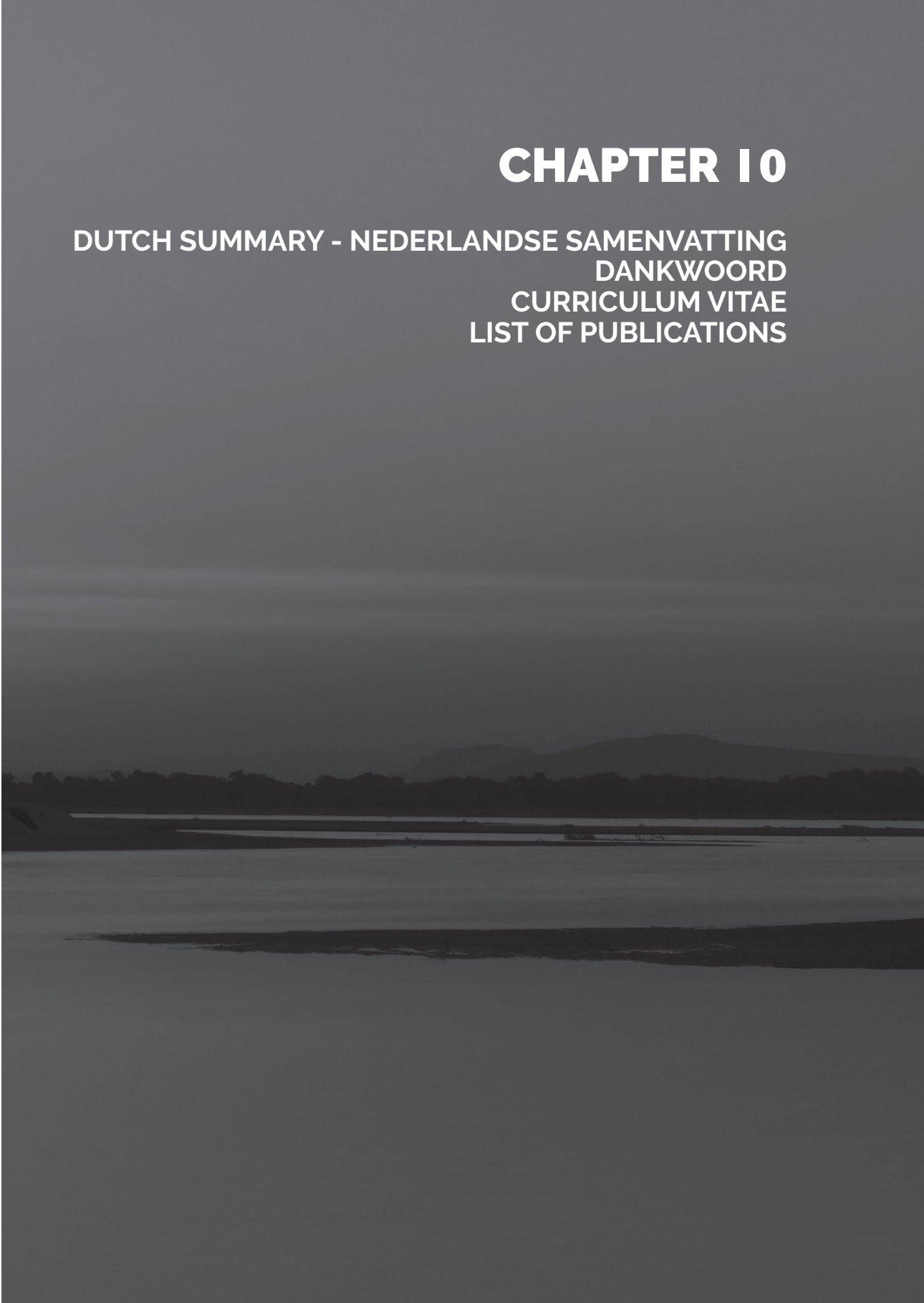
CHAPTER 10

DUTCH SUMMARY - NEDERLANDSE SAMENVATTING
DANKWOORD
CURRICULUM VITAE
LIST OF PUBLICATIONS



NEDERLANDSE SAMENVATTING

Gezonde nieren verwijderen overtollig vocht en afvalstoffen uit het bloed, regelen de mineralenhuishouding en produceren hormonen, zoals renine en erytropoëtine. Wanneer er geleidelijk schade aan de nieren of verslechtering van de nierfunctie ontstaat voor ten minste drie maanden, dan is er sprake van een chronische nierziekte. Dit heeft implicaties voor de gezondheid. Chronische nierziekten vormen een groot volksgezondheidsprobleem wereldwijd en komen voor bij meer dan 10% van de populatie.

Chronische nierziekten worden geclassificeerd op basis van de nierfunctie en de mate van eiwitverlies in de urine. Daarbij zijn vijf stadia te onderscheiden en hoe hoger het stadium hoe verder gevorderd de nierziekte is. Stadium 5 wordt ook wel eindstadium nierfalen genoemd en in dit eindstadium is nierfunctievervangende therapie nodig. Deze nierfunctievervangende therapie bestaat uit dialyseren of het ondergaan van een niertransplantatie. Een niertransplantatie wordt vaak verkozen boven dialyseren, omdat dit in het merendeel van de patiënten leidt tot verbetering van kwaliteit van leven en een verbeterde overleving. Vanwege bijkomende problemen zoals hart- en vaatziekten komen echter niet alle patiënten in aanmerking voor een niertransplantatie. Daarnaast is er een lange wachttijd (gemiddeld > 3 jaar in Nederland) door de beperkte beschikbaarheid van donororganen. Hierdoor zijn deze patiënten afhankelijk van dialyse. De huidige klinische richtlijnen adviseren dat patiënten met chronisch nierfalen tijdig, bij een nierfunctie van 30 ml/min/1.73 m^2 (stadium 4), worden verwezen naar een gespecialiseerde predialyse polikliniek. Deze zorg is gericht op het vertragen van progressie van de nierziekte en op de voorbereiding van het al dan niet starten met nierfunctievervangende therapie.

Dit proefschrift heeft tot doel om inzicht te verschaffen in zowel klinische als methodologische aspecten die van belang zijn bij het bestuderen wanneer gestart zou moeten worden met dialyse in patiënten met een gevorderde chronische nierziekte.

Om te kunnen anticiperen op de eventuele noodzaak van nierfunctievervangende therapie, is kennis over de snelheid van nierfunctieachteruitgang onontbeerlijk. In wetenschappelijke literatuur wordt een substantiële heterogeniteit gezien wat betreft de grootte van deze nierfunctieachteruitgang in patiënten met een chronische nierziekte. Deze heterogeniteit kan te wijten zijn aan variaties in patiëntkarakteristieken of de wijze waarop patiënten zijn geselecteerd in de cohortstudie. Globaal kan deze patiëntselectie op twee manieren plaatsvinden in studies naar de nierfunctieachteruitgang. De snelheid van nierfunctieachteruitgang kan prospectief bestudeerd worden vanaf een gemeenschappelijk punt in de ziekteprogressie in

patiënten met gevorderde chronische nierziekte, of kan retrospectief bestudeerd worden door dialysepatiënten te selecteren en in deze patiëntgroep de nierfunctiedaling in kaart te brengen over de periode voor de start van dialyse. In het laatste geval is de geschatte nierfunctieachteruitgang mogelijk niet representatief voor de werkelijke grootte van de nierfunctieachteruitgang van deze patiëntpopulatie. Daar wordt namelijk geen rekening gehouden met het feit dat patiënten in een vergevorderd stadium van chronische nierziekte ook nog kunnen herstellen of nooit met dialyse starten. In **hoofdstuk 2** laat een systematische review en meta-analyse van 60 studies zien dat de nierfunctiedaling, die prospectief is bekeken vanaf een gemeenschappelijk punt in de progressie van de nierziekte, beduidend kleiner is dan de nierfunctiedaling die retrospectief in de periode voor het dialyseren in de dialysepopulatie wordt verkregen. Wegens de vertekende weergave van de grootte van de nierfunctiedaling in deze laatste studiepopulatie is het van essentieel belang dat de nierfunctiedaling prospectief bestudeerd wordt en klinische besluitvorming op deze data berust.

Een tweede methodologisch aspect dat uitkomstparameters, zoals nierfunctiedaling of mortaliteit, kan beïnvloeden in cohortstudies is het moment in de ziekteprogressie waarop patiënten worden geselecteerd in een patiëntcohort. Stel we willen het effect van een abnormaal serum fosfaat op de mortaliteit in dialysepatiënten onderzoeken, dan kunnen dialysepatiënten op twee manieren geselecteerd worden. Patiënten kunnen vanaf de start van dialyse gevolgd worden, waarbij zij zich bevinden in hetzelfde ziektestadium maar een ander moment in de tijd. Dit noemen we een incident patiëntcohort. Daarentegen kunnen dialysepatiënten ook geselecteerd worden op bijvoorbeeld één moment in de tijd (op een specifieke datum) waarbij de patiënten al voor verschillende tijdsperioden aan het dialyseren zijn op het moment van start van de cohortstudie. Dit noemen we een prevalent patiëntcohort. Kwetsbare patiënten kunnen mogelijk al overlijden voordat het prevalente patiëntcohort wordt samengesteld. De invloed van de selectie van het patiëntcohort op effectschattingen van associaties tussen risicofactoren en uitkomsten is binnen de nefrologie niet empirisch onderzocht. **Hoofdstuk 3** toont aan dat de selectie van een prevalent versus incident patiëntcohort belangrijke verschillen laat zien in de grootte van effectschattingen voor de associatie tussen een reeks risicofactoren en de uitkomst mortaliteit in dialysepatiënten. Het mortaliteitsrisico blijkt voor de meerderheid van de risicofactoren lager te zijn in een prevalent cohort dan een incident cohort, echter soms werden zelfs tegengestelde effecten geobserveerd. Deze verschillen in resultaten zouden verklaard kunnen worden door het fenomeen selectiebias. Patiënten in een prevalent cohort moeten overleefd hebben tot een bepaald moment om geïncludeerd te kunnen worden in dit cohort. Kwetsbare patiënten die overlijden voordat een

prevalent cohort wordt geselecteerd zullen zijn blootgesteld aan meer mortaliteitsgerelateerde risicofactoren en de geselecteerde prevalente patiënten zijn geen willekeurige steekproef van alle patiënten uit een incident cohort. Wanneer nu een risicofactor-uitkomst associatie wordt bestudeerd, zullen prevalente patiënten met de bestudeerde risicofactor minder kans hebben op andere risicofactoren voor mortaliteit dan prevalente patiënten zonder de bestudeerde risicofactor: Om ondanks de blootstelling aan de bestudeerde risicofactor toch te overleven tot aan inclusie in het prevalente cohort zal een patiënt logischerwijs aan minder andere risicofactoren voor mortaliteit zijn blootgesteld. Deze fundamentele onvergelijkbaarheid zorgt voor vertekening in de schatting van de risicofactor-uitkomst associatie. Dit is het probleem van selectiebias. Het feit dat de patiëntselectie geassocieerd is met de risicofactor betekent niet noodzakelijkerwijs dat een vertekening van de resultaten van de risicofactor-uitkomst associatie optreedt. Wanneer er ook andere factoren zijn gerelateerd de patiëntselectie en aan de uitkomst (onafhankelijk van hun relatie met de risicofactor), kan selectiebias optreden. Alleen als al deze factoren adequaat gemeten zijn, zou voor al deze factoren gecorrigeerd kunnen worden en kan het probleem van selectiebias opgelost worden. Kortom, een zorgvuldige afweging voor de selectie van een incident versus prevalent cohort dient gepaard te gaan met de afweging op mogelijke vertekening van de resultaten op een onderzoeksvraag.

Een ander belangrijk methodologisch aspect na de patiëntselectie en dataverzameling is de manier van analyse van de data omtrent de nierfunctiedaling. Om de nierfunctieachteruitgang van een patiënt in kaart te brengen, wordt de patiënt in het cohort over het algemeen gevolgd over de tijd en wordt de nierfunctie op verschillende tijdspunten bepaald voor een bepaalde tijdsperiode. Sommige patiënten zullen eerder uit de studie vallen tijdens deze tijdsperiode dan anderen. Verder kunnen deze patiënten een variëteit aan nierfuncties laten zien aan het begin van het cohort, en ook de grootte van de nierfunctiedaling en het aantal beschikbare nierfunctiemetingen zal variëren. In **hoofdstuk 4** wordt duidelijk dat het belangrijk is om deze aspecten van heterogeniteit mee te nemen bij het bestuderen van de grootte van de nierfunctiedaling in associatie tot een risicofactor, diastolische bloeddruk in dit geval. Bij lineaire regressie wordt vanuit alle beschikbare nierfunctiemetingen per individu een daling berekend en in een tweede stap worden deze samengevat in een gemeenschappelijke daling voor de hele studiepopulatie in associatie tot diastolische bloeddruk. Daarbij worden slechts de individuen meegenomen met minimaal 2 nierfunctiemetingen en verschillen tussen individuen betreft het aantal beschikbare metingen en de lengte van de follow-up worden genegeerd. Dit alles vertekent de ware grootte van de associatie tussen diastolische bloeddruk en nierfunctiedaling. Linear mixed models behouden al deze informatie en variabiliteit in de data en bieden daarmee een betere schatting van de werkelijke associatie.

Naast deze methodologische aspecten, zijn ook veel klinische vraagstukken in patiënten met een chronische nierziekte nog onbeantwoord. Zo is het vanuit klinisch oogpunt te verwachten dat het aantal symptomen en de symptomenlast toenemen bij een verslechtering van de nierfunctie in patiënten met een chronische nierziekte. Echter, voor deze associatie bestaat geen wetenschappelijk bewijs. Uit cross-sectionele studies is tot nu toe gebleken dat nierfunctie en symptomen op één moment in de tijd over het algemeen niet met elkaar geassocieerd zijn. In **hoofdstuk 5** van dit proefschrift wordt voor het eerst aangetoond dat een snellere nierfunctiedaling over de tijd wel geassocieerd is met een grotere toename in symptomen, zowel in ernst als het aantal. Onze resultaten lijken te impliceren dat het in kaart brengen van de symptomenontwikkeling tijdens polikliniekbezoeken belangrijk is voor de klinische besluitvorming, naast het volgen van de nierfunctie. Naast deze samenhang tussen nierfunctiedaling en symptomentoename, weten we dat de nierfunctieachteruitgang samenhangt met risicofactoren, zoals hypertensie en diabetes mellitus. Zo zijn er ook verstoringen in de botmineralisatie geassocieerd met een snellere nierfunctieachteruitgang, zoals een hoog fosfaat. In **hoofdstuk 6** laten we zien dat een lager serum calcium in gevorderde stadia van chronische nierziekten geassocieerd is met een snellere nierfunctiedaling. Daarentegen blijkt deze associatie niet aanwezig te zijn als in stadium 3a met een nierfunctie tussen 45 en 60 ml/min/1.73m^2.

Kennis over progressie van chronische nierziekten is belangrijk om te kunnen anticiperen op wanneer eventueel gestart dient te worden met dialyseren. Het blijft echter onduidelijk wanneer patiënten met een gevorderd stadium het beste kunnen starten met dialyseren. Het is een balans tussen niet te vroeg starten om de last van het dialyseren zelf zo laag mogelijk te houden en niet te laat starten om complicaties van eindstadium nierfalen te voorkomen. Klinische richtlijnen geven aan om bij een nierfunctie van 5-10 ml/min/1.73m^2 te starten, mede afhankelijk van de aanwezigheid van symptomen. Tot op heden is slechts één gerandomiseerde studie uitgevoerd waarin geen verschil tussen vroeg of laat starten werd geconstateerd in termen van overleving.

Voorgaande observationele studies lieten geen eenduidige resultaten zien en werden gelimiteerd door methodologische aspecten, zoals lead-time bias en immortal time bias. Deze twee typen bias ontstaan wanneer de overleving vanaf het startmoment van dialyse wordt geteld. In het kort betekent lead-time bias dat een mogelijk overlevingsvoordeel wordt gezien bij patiënten die vroeg starten met dialyseren vergeleken latere starters, puur te wijten aan het feit dat de overleving in de vroege startgroep vanaf een eerder moment in de tijd wordt geteld dan in de late startgroep. In dit proefschrift laat **hoofdstuk 7** zien dat lead-time bias

niet alleen een methodologisch probleem is, maar ook een klinisch probleem in de vraagstelling wanneer gestart moet worden met dialyseren. Het overlevingsvoordeel voor vroege starters verdween na correctie voor lead-time bias.

Het feit dat patiënten alleen worden geïncludeerd in een cohortstudie als ze overleven tot zij gaan dialyseren, introduceert immortal time bias. Zowel lead-time bias als immortal time bias kunnen opgelost worden door een gerandomiseerde studie uit te voeren, omdat de overlevingsduur dan wordt geteld vanaf een gemeenschappelijk startmoment vóór de dialyse. Daarnaast worden individuen toegewezen aan een behandelarm voor het startmoment van dialyse, voordat zij daadwerkelijk starten met dialyseren. Idealiter zou het optimale startmoment bepaald worden in een gerandomiseerde studie met veel verschillende behandelarmen die alle mogelijke startmomenten bevatten. Echter het uitvoeren van een dergelijke trial is onhaalbaar, omdat een onredelijk groot aantal deelnemers nodig zou zijn om genoeg power te hebben om alle behandelarmen te kunnen vergelijken. Daardoor zijn we aangewezen op data van observationele studies. In **hoofdstuk 8** laten we aan de hand van een pilotstudie zien hoe observationele data gebruikt kunnen worden om een gerandomiseerde studie na te bootsen om het optimale startmoment van dialyse te vinden, zonder dat de resultaten beïnvloed worden door lead-time bias of immortal time bias. Onze pilotstudie bleek te klein in aantal patiënten om klinisch relevante conclusies te kunnen trekken wanneer gestart moet worden met dialyse. De bevindingen impliceren dat een grotere observationele studie nodig is met meer gedetailleerde informatie over de conditie/gezondheidstoestand van patiënten, waarin nierfunctieschattingen en confounders over de tijd geregistreerd zijn.

Toekomstperspectieven

Dit proefschrift laat de klinische impact van verschillende methodologische aspecten zien die in ogenschouw genomen dienen te worden om een antwoord te vinden op de vraag wanneer te starten met dialyseren.

Om een antwoord te verkrijgen op de hoofdvraag over het optimale moment van het starten met dialyse, zouden we idealiter een gerandomiseerde studie uitvoeren met daarin alle verschillende behandelarmen die alle mogelijke startmomenten voor dialyse bevatten. Het aantal patiënten benodigd om met voldoende power alle behandelarmen te vergelijken, maakt een dergelijke gerandomiseerde trial in de nabije toekomst onhaalbaar. We berusten daarom op data van observationele studies om een antwoord te vinden op onze vraag wanneer te starten met dialyse. Toekomstig onderzoek zou een grote observationele studie moeten beslaan met een grote studiepopulatie waarvan gedetailleerde informatie over de tijd gemeten is, inclusief

symptomen en de gezondheidstoestand van patiënten. Daarnaast zou een relatief lange follow-up periode nodig zijn, zodat voldoende individuen dialyseren en voldoende sterfgevallen geregistreerd zijn in de data voor het bereiken van voldoende power in alle behandelarmen. De resultaten van onze pilotstudie impliceren dat een lange follow-up periode nodig is met data van minimaal 1500 patiënten met een gevorderde chronische nierziekte, waarvan minimaal 300 sterfgevallen worden geregistreerd.

Voor het nabootsen van een gerandomiseerde studie met behulp van observationele cohortdata is één van de assumpties de afwezigheid van confounding by indication, een vorm van ongemeten confounding. Confounding by indication houdt in dat de klinische besluitvorming omtrent het startmoment van dialyseren wordt beïnvloed door de voorkeuren van artsen, (hun oordeel over) de conditie van een patiënt et cetera. Deze informatie is niet altijd beschikbaar in een observationele studie. Het voordeel van een gerandomiseerde studie is dat deze confounding by indication wordt geëlimineerd, omdat patiënten op basis van toeval aan een behandelarm worden toegewezen. Echter met observationele studies, die gebruikt worden om een gerandomiseerde studie na te bootsen, is het belangrijk om af te wegen of er voldoende informatie beschikbaar is om aan te nemen dat resultaten niet door confounding by indication worden beïnvloed. De algemene, bijna filosofische, vraag blijft of deze aanname valide gedaan kan worden, om zo het optimale startmoment van dialyse te bepalen. Uiteindelijk zou een klinische beslisregel, inclusief nierfunctie en symptomenontwikkeling, kunnen bijdragen om te anticiperen op het moment al dan niet te starten met dialyseren.

De vraag wat het optimale startmoment is voor dialyse blijft belangrijk en voor een groot deel nog onbeantwoord. Dit proefschrift laat methodologische aspecten en aanbevelingen zien die gebruikt kunnen worden om in de toekomst een definitiever antwoord te vinden.

DANKWOORD

Graag maak ik van de gelegenheid gebruik om iedereen te bedanken die op enige wijze heeft bijgedragen aan de totstandkoming van dit proefschrift.

Allereerst wil ik alle patiënten bedanken die hebben deelgenomen aan de verschillende studies die voor dit proefschrift zijn gebruikt. Zonder hun bereidheid om deel te nemen aan deze studies, zou het onderzoek dat in dit proefschrift is beschreven niet kunnen zijn uitgevoerd. Daarnaast wil ik graag alle onderzoekers bedanken die hebben geholpen bij het verzamelen van alle gegevens.

Dit proefschrift had niet tot stand kunnen komen zonder de hulp en steun van een groot aantal mensen. Allereerst wil ik graag mijn dank uitspreken aan mijn promotor Professor F.W. Dekker en co-promotores Dr. M. van Diepen en Dr. J.I. Rotmans. Bedankt voor jullie goede begeleiding en vertrouwen. Friedo, bedankt voor de vele goede ideeën, en je aanstekelijke enthousiasme voor epidemiologische vraagstukken. Joris, bedankt voor je enthousiasme en het klinische perspectief dat je met me hebt gedeeld. Merel, ik had mij geen fijnere dagelijkse supervisie kunnen wensen. Bedankt dat ik altijd bij je binnen mocht lopen, voor de prettige communicatie, je kritische blik, snelle feedback, en alle gezelligheid. Daarnaast wil ik natuurlijk alle coauteurs bedanken voor hun bijdrage.

Ik wil alle promovendi, stafleden en andere collega's van de afdeling klinische epidemiologie bedanken. Dankzij jullie is mijn promotietraject omgevlogen. Bedankt voor de vele leerzame momenten, de goede sfeer en gezellige koffiepauzes. Tamara en Yvonne, dank voor jullie goede zorgen en voor jullie hulp bij alle logistiek.

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Dear EQUAL colleagues, thank you all for the wonderful collaboration, the useful meetings and advices for doing research. I look forward to continue working together in the future to improve patient care for patients with advanced chronic kidney disease.

Bedankt Esmee en Esther, mijn paranimfen, voor jullie gezelligheid en ondersteuning in aanloop naar de verdediging, en op de dag zelf.

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CURRICULUM VITAE

Cynthia Jacomeine Janmaat werd op 24 juni 1991 geboren te Woerden. In 2009 behaalde zij haar gymnasiumdiploma aan het Minkema College in Woerden, waarna zij aan de studie Geneeskunde begon aan de Universiteit Leiden. In 2011 begon zij tevens met de pre-master Biomedische Wetenschappen aan de Universiteit Leiden. In 2012 behaalde zij het Honours College-Certificaat. In 2016 behaalde zij zowel haar master Geneeskunde als haar master Biomedische Wetenschappen cum laude. Tijdens haar studie Geneeskunde heeft zij zich verdiept in de Interne Geneeskunde, waar zij haar semi-arts stage liep en zij heeft haar wetenschappelijke stage op de afdeling Nierziekten gedaan. Tijdens haar master Biomedische Wetenschappen deed zij haar masterstage op de afdeling Klinische Epidemiologie, wat zij in 2016, na het verkrijgen van een 3-jarige promotiebeurs van de Raad van Bestuur van het Leids Universitair Medisch Centrum, voortzette in promotieonderzoek, onder supervisie van Prof. Dr. F.W. Dekker, Dr. M. van Diepen en Dr. J.I. Rotmans. In 2017 heeft zij voor haar masterscriptie de Dick Held Juniorprijs ontvangen. In dit proefschrift zijn de resultaten van het promotieonderzoek beschreven. De resultaten van dit onderzoek zijn door haar op verschillende nationale en internationale congressen gepresenteerd. Naast haar promotietraject was zij een van de Nederlandse coördinatoren van de EQUAL studie, een Europese studie naar het beste moment om dialyse te starten voor patiënten met een chronische nierziekte. Tijdens het promotietraject volgde zij verschillende epidemiologische cursussen voor de registratie tot Epidemioloog B. Daarnaast heeft zij onderwijs gegeven aan (bio)medische studenten, waaronder de Masterclass Klinische Epidemiologie in Noordwijk. Per 1 september 2019 is zij gestart als internist in opleiding in het Groene Hart Ziekenhuis in Gouda. Tenslotte is zij in mei 2019 moeder geworden van een dochter, Lune, en verloofd met haar partner, Kevin.

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This thesis

1. **Janmaat CJ**, van Diepen M, Gasparini A, Evans M, Qureshi AR, Arnlov J, Barany P, Elinder CG, Rotmans JI, Vervloet M, Dekker FW, Carrero JJ. Lower serum calcium is independently associated with CKD progression. Sci Rep. 2018;8(1):5148.
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11. Klatte DCF, Gasparini A, Xu H, de Deco P, Trevisan M, Johansson ALV, Wettermark B, Arnlov J, **Janmaat CJ**, Lindholm B, Dekker FW, Coresh J, Grams ME, Carrero JJ. Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease. Gastroenterology. 2017;153(3):702-710.
12. Voorzaat BM, **Janmaat CJ**, van der Bogt KE, Dekker FW, Rotmans JI. Patency of arteriovenous fistulas and grafts for hemodialysis access: a trade-off between non-maturation and long-term complications. Kidney360. 2020. doi:10.34067/KID.0000462020
13. van Diepen ATN, Coester AM, **Janmaat CJ**, Dekker FW, Struijk DG, Krediet RT Comparison between a conventional and a more biocompatible dialysis solution in incident peritoneal dialysis patients. *Submitted*