Nutritional status in chronic dialysis patients : associations with development of disease and survival

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General introduction

The main objective of this thesis was to study the association between nutritional status and survival in end-stage renal disease patients who are maintained on a chronic dialysis treatment. This general introduction will describe the epidemiology of chronic kidney disease and its progression to end-stage renal disease, the current state of knowledge about nutritional status in chronic dialysis patients, and how the chapters in this thesis may contribute to our understanding.

CHRONIC KIDNEY DISEASE

Chronic kidney disease is a large public health problem with a prevalence of around 10% in most populations.[1] Chronic kidney disease is characterized by failure of the kidneys to remove waste products and excess fluid from the body. Different degrees of renal dysfunction from the earliest kidney damage to end-stage renal disease have been classified into five stages on the basis of markers of kidney damage and level of kidney function (glomerular filtration rate).[2] The main causes of chronic kidney disease are diabetes mellitus, renal vascular diseases, glomerulonephritis and hypertension.[3] The risk of chronic kidney disease increases with ageing,[2] but also lifestyle factors may play a role in the development of chronic kidney disease. It is known that obesity leads to chronic kidney disease through diabetes mellitus and hypertension, but emerging evidence indicates that obesity may also contribute directly to kidney damage through a cascade of additional hemodynamic, metabolic, and inflammatory mechanisms as well as by mechanical compression.[4-15] In addition, there is evidence that smoking may be a risk factor for chronic kidney disease.[6;16;17] Furthermore, the prevalence of chronic kidney disease is 1.5 times increased in men compared with women,[3] suggesting a sex difference in susceptibility.

Yearly, a small proportion of patients with chronic kidney disease patients reach stage 5, end-stage renal disease, with estimates varying from 0.1 to 2.6 per 100 patients with stage 3 to 4 chronic kidney disease.[1;18] The overall incidence rate of end-stage renal disease is three times higher in the United States (339 per million population in 2004) compared with Northern Europe (110 per million population in 2004), possibly due to a higher prevalence of type 2 diabetes and to differences in

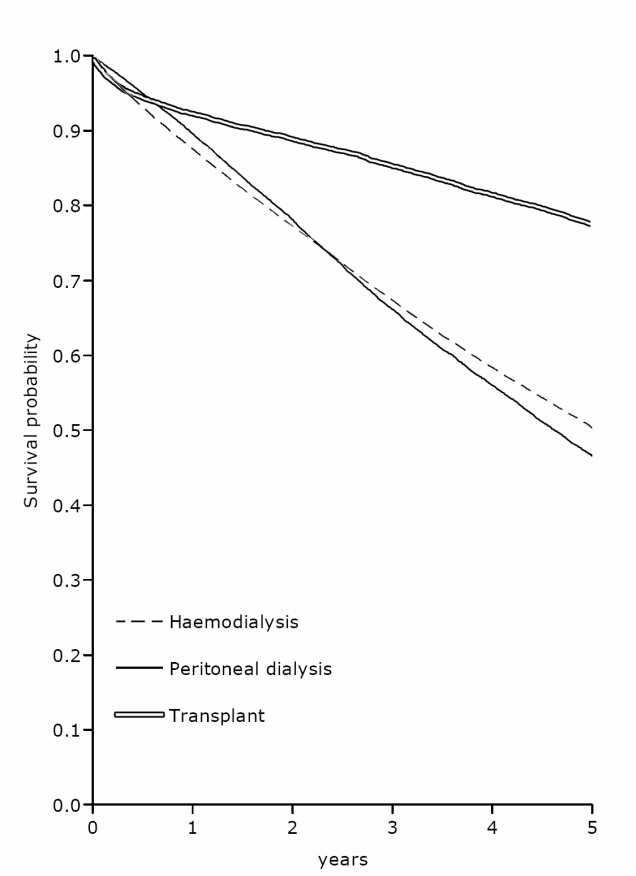

Figure 1. Survival of incident dialysis patients and patients receiving a first transplant in Europe (cohort 1996-2000), adjusted for age, gender and primary diagnosis.[3]

pre-dialysis care in the US population.[1;3;19;20] Once chronic kidney disease patients progress to end-stage renal disease, renal replacement therapy becomes necessary. Currently, there are about 440 000 prevalent patients registered in Europe who are maintained on a renal replacement therapy.[3;21] Kidney transplantation is the optimal renal replacement treatment for patients with end-stage renal disease. However, not all patients fulfill eligibility criteria to undergo surgery[22] and waiting lists for a matching kidney are long. Furthermore, the probability of graft failure ranges from 6 to 10% in the first year after transplantation,[3] after which dialysis treatment is (again) indicated. Dialysis has provided live-saving renal replacement therapy for patients with end-stage renal disease since the 1960s.[23] Although dialysis

techniques have improved ever since, the mortality of chronic dialysis patients remains alarmingly high world-wide,[24] with an annual mortality of about 20%.[21;25] The survival probabilities of patients with chronic kidney disease in the first five years after the start of hemodialysis treatment, peritoneal dialysis treatment, or after a first transplant in Europe (1996-2000) are shown in figure 1.[3]

NUTRITIONAL STATUS IN CHRONIC DIALYSIS PATIENTS

Nutritional status is one of the risk factors for mortality in chronic dialysis patients. Malnutrition can be defined as a state of nutrition in which an excess or deficiency of energy, protein and other nutrients causes measurable adverse effects on body composition, body function and clinical outcome.[26] Both overnutrition and undernutrition are highly prevalent in the dialysis population. The prevalence of obesity, defined as a BMI>30 kg/m^2 is estimated around 30% at the start of dialysis in the US.[27] The prevalence of undernutrition, defined as protein-energy wasting,[28] ranges between 29% and 48% at the start of dialysis, depending on the nutritional parameter that has been used.[29-33] Once on dialysis, the prevalence of protein-energy wasting ranges between 23 and 76% in hemodialysis patients and between 18 and 50% in peritoneal dialysis patients.[29;30;34-42] Approximately 10% of these patients suffers from severe protein-energy wasting.[43] The following paragraphs will first describe the obesity-survival paradox and second the current knowledge about protein-energy wasting in the dialysis population.

Obesity-survival Paradox

Whereas obesity is one of the established risk factors for increased morbidity and mortality in the general population,[44-47] many survival studies in hemodialysis patients, however, have indicated opposite associations of obesity.[48-55] Low values for body mass index (BMI) are associated with increased mortality, and higher values for BMI, even morbid obesity, were found to be protective and associated with improved survival in dialysis patients (Figure 2). This obesity-survival paradox in the dialysis population has been referred to as 'reverse epidemiology[56;57] and has led to the hypothesis that a higher level of adiposity may provide a survival

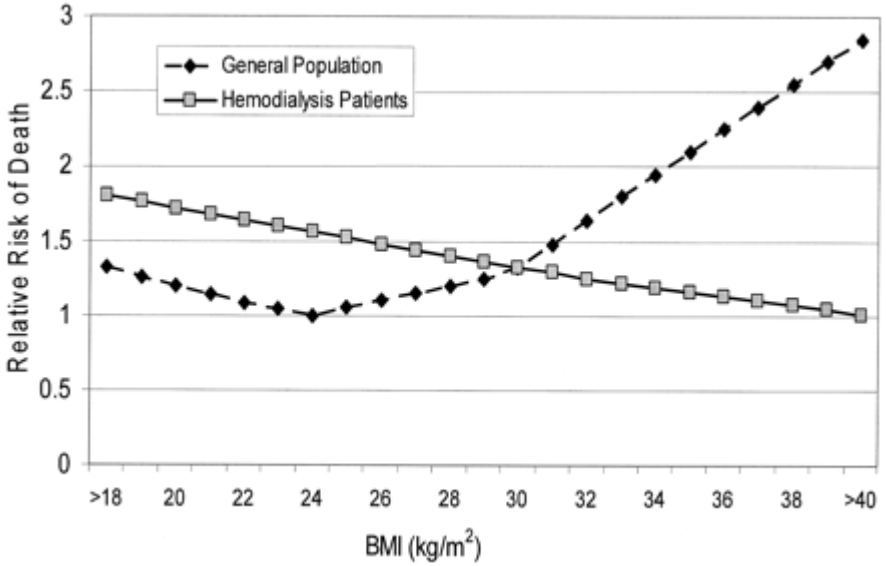

Figure 2. Reverse epidemiology of obesity in dialysis patients compared with the general population. Comparison between the effects of BMI on all-cause mortality in the general population and in the maintenance hemodialysis population. Note that each population has a different follow-up period: 14 y for the general population compared with 4 y for the hemodialysis patients.[57]

advantage for patients with end-stage renal disease.[49;58] This hypothesis has generated much debate about the plausibility of the observed associations and the application of these findings in every day practice.[59-61] Several explanations have been suggested to explain the 'reverse epidemiology' of BMI and mortality in dialysis patients: 1) time-discrepancies between the competing risks of adverse events that are associated with overnutrition and undernutrition,[58] 2) a dominant role of wasting in chronic disease states or reverse causation,[56;62] 3) a selected genotype resulting from survival selection during the course of chronic kidney disease progression,[56;63] 4) a more stable hemodynamic status,[56] 5) alterations in circulating cytokines,[56] 6) an endo-toxin-lipoprotein interaction,[56;64] 7) a lower uremic toxin production rate in obesity.[65] However, exact reasons remain unclear. It must be noted that the BMI-mortality association in the general population is based on results from middle-aged populations that have been followed for more than ten years, whereas the dialysis population is older on average and is generally followed

for not more than 2-4 years as a result of the high mortality rate. Thus, short-term mortality in dialysis patients is compared with long-term mortality in the general population. We hypothesized that the age of the patients and the duration of follow-up influences the BMI-mortality association in these patients.

Protein-energy Wasting

Definition of Protein-energy Wasting

No uniform definition of undernutrition exists. Two main types of primary malnutrition have been described as a consequence of inadequate dietary intakes with distinct clinical symptoms: kwashiorkor because of protein depletion, and marasmus because of a depletion of both protein and energy stores.[66;67] Secondary to chronic diseases, often signs of both kwashiorkor and marasmus are found, which has been referred to as protein-energy malnutrition.[66;68] This disease-related malnutrition can be defined as a lack in supply of sufficient energy or protein to meet the body's metabolic demands as a result of either an inadequate dietary intake of protein, intake of poor quality dietary protein, increased requirements because of disease, or increased nutrient losses.[43] In 2007, an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) recommended the term 'protein-energy wasting' to indicate loss of body protein mass and fuel reserves in chronic kidney disease.[28] In this thesis, the term protein-energy wasting is used to indicate an undernourished state in dialysis patients, according to this recommendation. In the chapters written before the publication of this recommendation the term malnutrition should be read as protein-energy wasting.

Causes of Protein-energy Wasting

A schematic representation of the possible causes of a decreased nutritional intake and increased nutritional requirements resulting in protein-energy wasting in chronic kidney disease is shown in Figure 3.

In pre-dialysis stages chronic kidney disease patients are advised to reduce their protein intake in order to improve uremic symptoms and to slow the progression to kidney failure.[69-71] Besides this advised dietary protein restriction, the protein intake of chronic kidney disease patients spontaneously reduces as renal function

declines.[72-74] A loss of appetite, nausea and vomiting accompany this uremia-induced anorexia.[75] Other causes of an inadequate dietary intake in these patients include medications, concurrent chronic illnesses, low socio-economic status of the patients and psychological depression.[41]

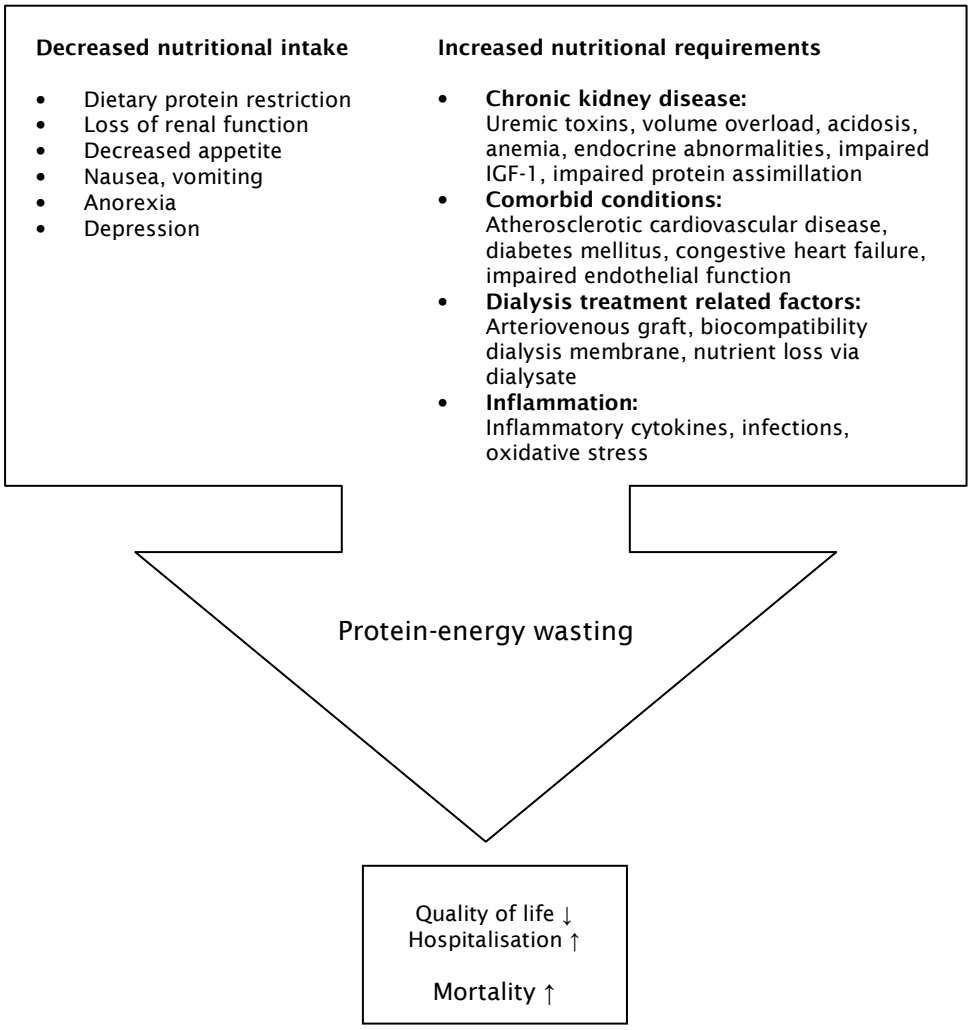

Figure 3. Schematic representation of the possible causes and consequences of protein-energy wasting in chronic kidney disease.

Besides an inadequate dietary intake many factors may increase nutritional requirements once patients are maintained on a chronic dialysis treatment.[76;77] The basal energy expenditure is increased in dialysis patients, thereby increasing energy requirements.[78;79] The dietary protein requirements of dialysis patients are increased because of the loss of amino acids and proteins through the dialysate, and also because of catabolic effects of the disease and dialysis procedure.[41;43;80] Catabolic effects of metabolic acidosis, inflammation and other comorbid conditions, altered amino acid and protein metabolism, hormonal derangements, endocrine disorders and impaired metabolic functions of the kidney stimulate muscle protein degradation via proteolytic pathways.[41;81-86] Furthermore, small intestinal protein assimilation (digestion and absorption) appears impaired in dialysis patients,[87] which may contribute to increased dietary protein requirements. Then, the dialysis procedure itself may confer a catabolic state by means of decreasing the circulating amino acids, accelerating rates of whole body and muscle proteolysis, stimulating muscle release of amino acids, and elevating net whole body and muscle protein loss.[80] All together, these factors may result in a negative nitrogen and energy balance, and consequently result in muscle mass depletion and unintentional weight loss, important characteristics of protein-energy wasting.

Consequences of Protein-energy Wasting

One of the first studies relating a poor nutritional status to mortality in chronic dialysis patients studied 48 chronic dialysis patients over a two-year period.[88] On the basis of nutritional parameters patients were given a score from 0 ('normal nutritional status') to 8 ('severe protein-caloric malnutrition') at start of the observation. After two years of follow-up the nutritional score was lower among the 39 surviving patients than among the nine patients who died. The authors concluded that chronic dialysis patients with a poor nutritional status have a highly increased mortality and recommended the prevention of protein-caloric malnutrition among dialysis patients as a high priority task.[88] Numerous observational studies have investigated the association of nutritional status with outcome since and related a poor nutritional status to functional limitations,[89] decreased quality of life,[90-92] increased morbidity,[38;93-96] and mortality.[49;93;94;97-106] However, most studies described small sample sizes or prevalent populations, or

used baseline assessments of nutritional status only. It furthermore remains unclear which parameter(s) may best represent a patient's nutritional status.

Assessment of Protein-energy Wasting

In addition to technical examinations, many clinical and laboratory parameters exist to measure the nutritional status of dialysis patients.[43;107] However, they all capture a different aspect of the nutritional status. Furthermore, many parameters are influenced by the kidney disease, hydration status of the patient or other comorbid conditions that may significantly alter nutritional indices irrespective of changes in true nutritional status.[108] The most commonly used nutritional parameters in the dialysis population and their advantages and disadvantages are listed in Table 1.

Reference standards such as magnetic resonance imaging, total body potassium, or total body nitrogen are often too expensive and time-consuming to use in large survival studies. Therefore, surrogate measures are necessary. It may be evident from Table 1 that a single marker of nutritional status may not be sufficient. According to the ISRNM expert panel, at least three characteristics need to be present to diagnose protein-energy wasting: 1) low serum levels of albumin, pre-albumin or cholesterol, 2) reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), and 3) reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference).[28] However, there is need for one simple, rapid, inexpensive instrument to assess the nutritional status in clinical practice. The Subjective global assessment of nutritional status (SGA) consists of a clinical judgment on the basis of four subscales representing the patients' recent weight change, dietary intake and gastro-intestinal symptoms, loss of subcutaneous fat, and signs of muscle wasting.[109-111] The SGA may therefore be a candidate measure that provides a comprehensive evaluation of the nutritional status in order to diagnose protein-energy wasting.

Table 1. Commonly used nutritional parameters in chronic dialysis patients: validity, advantages, disadvantages and feasibility in large studies.

	Measure of	Validity	Advantages (+) or disadvantages (-)	Feasibility in large studies
Technical examinations			- All: expensive, time-consuming, invasive for patients	
Magnetic resonance imaging	Body composition	Very high		Very low
Deuterium dilution	Total body water	Very high		Very low
Total body potassium	Body cell mass	Very high		Very low
In vivo neutron capture analysis	Total body nitrogen	Very high		Very low
Body densitometry	Body composition	High	- Assumes constant composition fat free mass[138]	Very low
Dual energy X-ray absorptiometry	Bone and soft tissue composition (fat and fat-free)	High	- influence hydration status on estimation of fat-free mass[138]	Intermediate
Bioelectrical impedance analysis	Total body water	High	- Influence of hydration status on estimation of fat-free mass[138]	Intermediate
Clinical parameters				
Body weight, BMI	Body fatness	Intermediate	- Cannot distinguish body fat, muscle mass or water[139]	Very high
Skinfold thickness	Body fat mass	Limited by assumptions of fat distribution, hydration status and inter-observer error[139;141-143]	+ Simple, inexpensive, rapid[142-144]	High
Mid-arm muscle area	Body muscle mass			High
Dietary diaries	Dietary intake	Limited by overestimation daily intake[145]	- Cumbersome for patients	Low
Hand-grip muscle strength	Muscle strength	High[32]	+ Parameter of physical functioning - no predictor of outcome in women[106]	High

	Measure of	Validity	Advantages (+) or disadvantages (-)	Feasibility in large studies
7-point SGA	Recent weight change, dietary intake and GI symptoms, loss of subcutaneous fat mass and muscle wasting	Valid and reliable [101;109;146] Recommended to detect severe protein-energy wasting[107]	+ May represent the overall concept of nutritional status	High
Laboratory parameters				
Serum albumin concentration	Visceral protein concentration, protein intake, inflammation	Limited by influence of inflammation, hepatic synthesis and degradation, metabolic acidosis, insulin resistance, hydration status, losses via urine and the dialysate [132;133;147;148]	- Negative acute phase reactant	Very high
Serum prealbumin concentration	Protein intake and visceral protein generation	Limited by influence inflammation	- Negative acute phase reactant	Very high
Serum cholesterol concentration	Serum cholesterol	Intermediate	- Influenced by lipid lowering medication and inflammation	Very high
Serum creatinine concentration	Protein intake and muscle mass (breakdown product of muscle metabolism)	Low	- Urinary creatinine excretion needs to be considered in nonanuric patients	Very high
Insuline-like growth factor-I	Anabolic hormone that has been related to lean body mass[149]	Intermediate	- influenced by age and inflammation	Very high
nPNA	Estimated protein intake from nitrogen balance	Valid in clinically and metabolically stable patients	- Overestimation protein intake in catabolic situations[150]	Very high

BMI=Body mass index, SGA=Subjective global assessment of nutritional status, GI symptoms=Gastro-intestinal symptoms (loss of appetite, nausea, vomiting and diarrhea), nPNA=normalized Protein Nitrogen Appearance

The MIA Syndrome

During the past decade, the important role of inflammation in the development of protein-energy wasting in chronic kidney disease has been recognized.[31;41;112]

Chronic inflammation is highly prevalent in the dialysis population and defined as a subclinical systemic inflammatory state of the patient characterized by increased concentrations of acute phase proteins as serum C-reactive protein (CRP) and pro-inflammatory cytokines as interleukin(IL)-6, IL-10 and tumor necrosis factor-α.[99;113-117] The causes of inflammation in dialysis patients remain to be resolved. Comorbid conditions, chronic infections and accumulation of advanced glycation end products may play a role.[96] Furthermore, the dialysis procedure itself may be responsible for an inflammatory response.[118]

Inflammation, mediated by pro-inflammatory cytokines, may be associated with an increase in protein catabolism, predisposing to protein-energy wasting in chronic kidney disease.[31] Several studies have shown that concentrations of pro-inflammatory cytokines were associated with basal metabolic rate, appetite and food intake, and muscle wasting.[112;119-121] Chronic inflammation has furthermore been associated with increased cardiovascular comorbidity and mortality, suggesting that inflammatory processes may have a role in both the pathogenesis of atherosclerotic cardiovascular disease and the development of protein-energy wasting in chronic kidney disease patients.[31;122-126] On the basis of the strong associations observed between malnutrition, inflammation and atherosclerosis in the dialysis population, Stenvinkel et al. have proposed that these risk factors may be pathophysiologically linked and thereby constitute a syndrome that carries a high mortality rate.[31;122;125] This syndrome has been referred to as the malnutrition, inflammation and atherosclerosis (MIA) syndrome.[125] Many studies have shown since that malnutrition, inflammation and cardiovascular diseases were interrelated, each contributing to the high mortality in dialysis patients.[99;113;127-131] However, at the best of our knowledge, it is unknown whether these three risk factors are independent risk factors or whether they interact, together resulting in an even higher mortality.

OBJECTIVES AND OUTLINE OF THE THESIS

The main objective of this thesis was to further study the association between nutritional status and survival in end-stage renal disease patients who are maintained on a chronic dialysis treatment. To place this objective in perspective, we first studied the associations of obesity with the development of chronic kidney disease in the general population and with mortality in the dialysis population. The major part of this thesis investigated the mortality risks of a poor nutritional status as estimated with nutritional parameters such as body mass index (BMI), skinfold thickness, serum albumin and the Subjective global assessment of nutritional status, including interactions with other comorbid conditions. The outline of this thesis will be as follows:

The study in **chapter 2** of this thesis estimated the risks of lifestyle factors, e.g. obesity, physical inactivity and smoking on the development of chronic kidney disease in a health survey of the general population and investigated whether these risks are greater in men than in women.
We hypothesized that the age of the patients and the duration of follow-up influences the BMI-mortality association in chronic dialysis patients, and therefore examined the association between BMI and mortality in the hemodialysis population and the general population when age and duration of follow-up were made strictly comparable in **chapter 3**.
Because BMI can not distinguish between fat mass and muscle mass we studied whether the increased mortality risk associated with a low BMI was due to a low fat mass or due to a low muscle mass, using skinfold measurements in **chapter 4**. We furthermore hypothesized that pre-existing comorbidity and weight loss partly explain the high mortality associated with a low BMI in the dialysis population in **chapter 4**.
In **chapter 5** we studied to what extent the association between serum albumin and mortality was mediated by nutritional status or by inflammatory status. Although it is known for many years that serum albumin is a negative acute phase reactant,[132;133] it is considered as a useful indicator of protein-energy nutritional status in dialysis patients and mentioned in current guidelines,[107] mainly because of its strong

association with outcome.[43] It is yet unclear whether the association between serum albumin and mortality in dialysis patients is only in response to inflammation or also - in part - a consequence of malnutrition.

In **chapter 6** we studied the association of the 7-point Subjective global assessment of nutritional status (SGA) with mortality in the dialysis population. For this study, the SGA had been assessed every six months of follow-up, allowing the estimation of both long-term and time-dependent risks of mortality.

Chapter 7 addresses the MIA syndrome in the dialysis population. We examined the presence of causal interaction between protein-energy wasting, inflammation and cardiovascular disease in the association with mortality in chronic dialysis patients in order to investigate whether these are three independent risk factors, or whether they interact and thereby result in a higher mortality than expected.

The concept of causal interaction between risk factors is explained in **chapter 8** and several measures are presented to examine the presence of interaction in applied data analysis.

Finally, in **chapter 9** we will reflect on the strengths and limitations of our findings and we will translate our findings into implications and recommendations for future research.

STUDY DESIGNS AND DATA USED IN THIS THESIS

For the majority of our research questions we used data from the Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD-II), a prospective, longitudinal, observational multi-center cohort study that has been performed since 1997 in 38 dialysis centers in The Netherlands. Patients with end-stage renal disease who were 18 years of age or older, understanding the Dutch language and starting with their first renal replacement therapy were invited to be included in NECOSAD-II.[134;135] Measures of health and nutritional status were recorded at three months and six months after the start of dialysis and subsequently at intervals of six months until the end of follow-up. In January 2007, 1940 ESRD patients had been included and followed for more than seven years after the start of dialysis until the date of death, the date of lost to follow-up because of kidney transplantation or transfer to a non-participating dialysis centre, the end of the

follow-up at the 1st of January 2007, or at a set maximum of follow-up for all patients.

For the research question in chapter 2 we collaborated with the Nord-Trøndelag Health Study 1995-97 (HUNT-II). The HUNT-II Study is a large, population-based, cross-sectional study that was conducted in central Norway with a participation rate of 70.6%.[136] In this health survey of the entire adult population of Nord-Trøndelag County, Norway 30,485 men and 34,708 women were included.[136]

For the research question in chapter 3 we collaborated with the Hoorn Study. Hoorn is a town with 60,000 inhabitants in the northwest part of The Netherlands. The Hoorn Study is a Dutch population-based prospective cohort study of glucose metabolism among 2484 healthy Caucasian adults, aged 50 to 75, which started in 1989.[137]

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