Chapter 1

General Introduction
GENERAL INTRODUCTION

This thesis is about depressive and anxiety symptoms in chronic dialysis patients and medically ill patients. It is divided in two parts, part A focuses on differences in the prevalence of depressive and anxiety symptoms in native and immigrant (chronic dialysis) patients and various factors (patient characteristics and cultural factors) associated with these symptoms. Part B focuses on the association of inflammation and depressive symptoms in chronic dialysis patients. The results may lead to more insight in the development of depressive and anxiety symptoms. In this chapter background information on end-stage renal disease (ESRD), depressive symptoms, immigrant status, patient characteristics/cultural factors, and inflammation/tryptophan degradation will be provided. Finally, the objectives and outline of this thesis will be described.

End-stage renal disease and chronic dialysis treatment

The kidneys have important endocrine, excretory and metabolic functions. Therefore, failing kidney function has significant consequences for health. When abnormalities of kidney structure or function are present for at least 3 months with implications for health it meets the definition of Chronic Kidney Disease (CKD). CKD is classified into 5 stages based on the presence of markers of kidney damage and level of kidney function. ESRD is the most severe form of CKD, defined by an estimated glomerular filtration rate (eGFR) below 15mL/min/1.73m².

In case of ESRD renal replacement therapy (RRT) is necessary to sustain life. In 2014 the prevalence rate of RRT in the Netherlands was 967 per million population (pmp). RRT can be provided by both kidney transplantation or chronic dialysis treatment. For many patients transplantation is the most favorable treatment, but due to shortage of transplantable kidneys or medical contraindications most patients depend on chronic dialysis treatment. Two types of chronic dialysis treatment can be distinguished, namely hemodialysis and peritoneal dialysis. In hemodialysis, waste products are removed by diffusion through a semi-permeable membrane in an extracorporeal device. In peritoneal dialysis, waste products are exchanged from the blood across the abdominal peritoneal membrane which operates as a dialysis membrane. Both types are known as intensive and time-consuming treatments with high morbidity and mortality rates.

Depressive symptoms in chronic dialysis patients

Depressive symptoms are common in chronic dialysis patients and are strongly associated with an increased risk of morbidity and mortality. The prevalence of depressive symptoms varies widely in existing studies, because of the use of different assessment tools. In a meta-analysis in 2013 a summarized prevalence of depressive symptoms of 39% was found. Depressive symptoms in chronic dialysis patients are difficult to recognize, due to overlap of uremic symptoms with (somatic)
symptoms of depression\textsuperscript{13}. Depressive symptoms are often undertreated and in addition, treatment of depression in case of a chronic illness is also more difficult\textsuperscript{14}.

The definition of a major depressive disorder according to the DSM-IV is: “Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks, in combination with four additional symptoms (such as eating problems, loss of energy or insomnia)”\textsuperscript{15}. To diagnose a depressive disorder a structured interview must be performed by a trained interviewer, preferably a psychiatrist. However, for research and screening in large groups of people mostly self-report questionnaires are used, because this is less time-consuming and can be provided by other caregivers. These questionnaires score the severity of depressive symptoms and by using a cut-off point an indication can be given of the presence or absence of a depressive disorder. A well-validated measure in dialysis patients is the Beck Depression Inventory (BDI)\textsuperscript{16}. This questionnaire has been validated in the dialysis department in OLVG west (Amsterdam)\textsuperscript{17}, one of the participating dialysis centers of the DIVERS study. The BDI includes both somatic and cognitive depressive symptoms and performs equally well to a questionnaire not including somatic symptoms\textsuperscript{17}.

Anxiety symptoms often coexist with depressive symptoms\textsuperscript{18} and the prevalence in chronic dialysis patients ranges from 13 to 50\%\textsuperscript{13;19;20}. In CKD patients a trend was found for an increased risk of poor clinical outcome (death or initiation of dialysis therapy)\textsuperscript{21}.

**Immigration in the Dutch setting**

The research in this thesis has been performed in the Netherlands. In western countries the number of non-native citizens increased significantly over the last decades due to immigration\textsuperscript{22}. The Netherlands became an immigration country after World War II, with immigration of guest workers (especially Turkish and Moroccan men) and immigrants from former colonies (such as Surinam or Indonesia)\textsuperscript{23;24}. Therefore, the largest groups of non-western migrants in the Netherlands are from Indonesia, Turkey, Morocco and Surinam, but over 200 different nationalities live in the Netherlands\textsuperscript{25}. Due to the growing number of especially non-western migrants interest in the association between immigrant status and (mental) health increases\textsuperscript{27}.

According to Statistics Netherlands, an immigrant is defined as an individual with at least one parent born abroad, regardless of their own country of birth\textsuperscript{29}. Immigrants can be divided in first generation immigrants, if the individual was born abroad, or second generation immigrants, if the individual was born in the Netherlands\textsuperscript{29}. In this way, a distinction is made in native and immigrant. As a large proportion of the ethnic minority groups in the Netherlands are first generation immigrants, country of birth is an appropriate classification\textsuperscript{27}. In this thesis patients are distinguished in two groups by using the country of birth definition: native (or native Dutch) and immigrant patients or white and non-white patients. The distinction in white and non-white patients is used for the examination of biochemical parameters (inflammatory markers
and tryptophan). Race (white/non-white) differs from immigrant status as it refers to physical characteristics of the patients.

**Part A: Patient characteristics and cultural factors**

Besides the high prevalence of depressive symptoms in chronic dialysis patients, also in other medical settings the prevalence of depressive symptoms is high. This high prevalence is probably caused by stressful experiences for medically ill patients, such as medical interventions, a hospital admission and uncertainty about the diagnosis. In the general population it has been found that the prevalence of depressive symptoms is higher in immigrants compared to natives. It is unclear whether in the hospital wide setting or for chronic dialysis patients, with already a high prevalence of depressive symptoms, immigrant status plays a role.

In the general population possible explanations for these differences in prevalence between natives and immigrants have been studied, but are not yet understood. Factors that possibly contribute a the higher presence of depressive symptoms in immigrants are a low socio-economic status, lower educational level and unemployment, ethnic discrimination, social exclusion, and migration-stress. Migration-stress may be interpreted and defined in different ways, and exists of different stages (pre-migration, initial stage, middle stage, and final stage/post-migration). In the final stage the process of acculturation begins. This term refers to the adaptation of an individual to a new cultural context as a result of migration. An individual’s acculturation status is associated with mental health. A review including population studies found less mental health problems when individuals participate in the new society, while containing their own culture.

Religion may help immigrants to retain or develop their identity during their integration in a new society. For chronic dialysis patients religion may help to cope with the stressful burden of dialysis treatment. However, in a cohort of dialysis patients in Brazil, also negative effects of religious coping on depressive symptoms have been found. Namely, negative religious coping was associated with more depressive symptoms. For immigrant chronic dialysis patients religion might have a different impact on depressive symptoms compared to native patients. It has not been examined what the effect of acculturation and religion is on depressive symptoms in immigrant chronic dialysis patients.

It is important to explore differences in the prevalence of depressive symptoms between native and immigrant (chronic dialysis) patients, so health care can be adapted to both groups. Furthermore, if factors responsible for differences in prevalence can be identified, the development of depressive symptoms may be prevented.
Part B: Inflammation and tryptophan degradation

In addition to the high prevalence of depressive symptoms, chronic dialysis patients are also known for an increased inflammatory state. This increased inflammatory state is due to an increased production of cytokines and decreased renal clearance. High inflammatory markers in chronic dialysis patients are associated with more depressive symptoms. The mechanism behind this association is not entirely clear. It has been proposed that tryptophan degradation along the kynurenine pathway might cause the development of depressive symptoms. Inflammatory markers activate the enzyme Indoleamine-2,3-dioxygenase (IDO), which degrades tryptophan (TRP) into its degradation product kynurenine (KYN) (figure 1). Therefore, a lower concentration of TRP is available to produce serotonin (5-HT). A lower concentration of 5-HT in the central nervous system may cause depressive symptoms. In addition also metabolites of KYN (Kynurenic acid (KA), Quinolinic acid (QA) and 3-hydroxy-kynurenine (3-OH-KYN)) itself may cause depressive symptoms.

![Figure 1. Tryptophan degradation along the kynurenine pathway.](image)

In chronic dialysis patients increased tryptophan degradation has been found compared to healthy individuals, with a lower TRP concentration and higher KYN concentration (and degradation products). Therefore, TRP degradation along the KYN pathway could well be responsible for the association between inflammatory markers and depressive symptoms in chronic dialysis patients.
The above described theory suggests that inflammation causes depression, instead of depression causing inflammation. However, in the general population multiple longitudinal studies also found evidence that depression may precede inflammation\textsuperscript{51-54}, and also a bidirectional relationship has been found\textsuperscript{55}. In chronic dialysis patients many studies examined cross-sectional associations between inflammation and depressive symptoms\textsuperscript{46}, but no longitudinal studies have been performed. Therefore, the causality of the inflammation-depression association in chronic dialysis patients is not clear. As the inflammatory status of chronic dialysis patients is increased compared to healthy individuals, results from the general population cannot be applied directly to the dialysis population. Research on the inflammation-depression and tryptophan-depression association in chronic dialysis patients may help us to understand the high prevalence of depressive symptoms in this patient group and may deliver specific targets for treatment.

Finally, racial differences have been found in the inflammation-depression association in general populations in the US\textsuperscript{56,57}, but contradictory results have been found. One study found stronger inflammation-depression associations in blacks\textsuperscript{56}, while another study found an association only in white women\textsuperscript{57}. In addition to these conflicting results, also the differing ethnic composition in the US compared to Europe makes it interesting to examine racial differences in the inflammation-depression association in the Netherlands as well. Also, a possible explanation for the ethnic differences in the prevalence of depressive symptoms may be found in biochemical factors (inflammatory markers and tryptophan).

Objective and outline of this thesis
In part A of this doctoral thesis we describe differences in the prevalence of depressive and anxiety symptoms in immigrant and native (chronic dialysis) patients and whether patient characteristics and cultural (acculturation and religion) factors are associated with these symptoms. In part B, the association between inflammatory markers and depressive symptoms in chronic dialysis patients and the role of tryptophan degradation is described.

Part A
In chapter 2 the prevalence of psychological distress (i.e. depressive and anxiety symptoms) was examined in the hospital wide setting. With specific focus on possible differences in prevalence of psychological distress between native and immigrant patients and between first and second generation immigrants. We explored whether possible differences could be explained by patient characteristics (such as demographic variables and socio-economic status). In chapter 3 the prevalence of depressive and anxiety symptoms in native and immigrant chronic dialysis patients was examined, also exploring whether differences could be explained by patient characteristics.
Subsequently, we examined in chapter 4 whether acculturation is a risk factor for more depressive and anxiety symptoms in immigrant chronic dialysis patients. In chapter 5 the effect of religious behavior and religious coping on depressive and anxiety symptoms in both native and immigrant chronic dialysis patients was examined.

Part B
In chapter 6 we examined the role of tryptophan degradation in the association between inflammatory markers and depressive symptoms in chronic dialysis patients. To examine the direction of the inflammation-depression association and long-term effects we performed in chapter 7 a longitudinal study. chapter 8 explored whether racial differences exist in the inflammation-depression and tryptophan-depression associations in chronic dialysis patients.

Finally, in chapter 9, the results of the previous chapters are discussed and summarized.

Data used in this thesis
The study described in chapter 2 was based on data collected in 2011 in most departments in OLVG west (formerly Sint Lucas Andreas hospital), a general teaching hospital in Amsterdam west, the Netherlands.

Data used in the other chapters are part of the DIVERS study, an observational prospective cohort study among prevalent and incident chronic dialysis patients in four urban teaching hospitals and one university hospital in Amsterdam and The Hague, the Netherlands. These hospitals were selected because of their large proportion of ethnic minority patients. DIVERS started in May 2012 and inclusion of prevalent and incident dialysis patients ended in December 2013 and July 2016 respectively.
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