Chapter 9
General Discussion
GENERAL DISCUSSION

This thesis is about depressive and anxiety symptoms in chronic dialysis patients and medically ill patients. Part A focused on differences in the prevalence of depressive and anxiety symptoms in native and immigrant patients and various factors (patient characteristics and cultural factors) associated with these symptoms (chapter 2-5). Part B focused on the association of inflammation and depressive symptoms in chronic dialysis patients (chapter 6-8). In this final chapter the results of the performed studies are summarized and discussed. Finally, the clinical implications of the results and suggestions for further research are provided.

Part A: Patient characteristics and cultural factors

Main findings

In chapter 2, the prevalence of psychological distress in a general teaching hospital in Amsterdam was explored, comparing 319 immigrant and 585 native patients. A high overall prevalence of psychological distress of 58% was found. Immigrant patients were 1.7 times more likely to have psychological distress (i.e. depressive and anxiety symptoms) compared to native Dutch patients. The prevalence was especially high in Turkish and Moroccan patients, 79% and 73% respectively. When comparing first and second generation immigrants, first generation immigrants were 2.1 times more likely to have psychological distress. Adjustment for patient characteristics (e.g. socio-economic status) did not explain these differences in psychological distress for both immigrant versus native patients and first versus second generation immigrants.

Subsequently, using the DIVERS study we examined whether in chronic dialysis patients the prevalence of depressive and anxiety symptoms also differed between 249 immigrant and 245 native patients (chapter 3). Immigrant chronic dialysis patients were 1.8 times more likely to report depressive symptoms compared to native chronic dialysis patients and 1.7 times more likely to report anxiety symptoms. In the immigrant patient group the highest prevalence for both depressive and anxiety symptoms was found in Asian patients. Patient characteristics (i.e. socio-demographic and clinical) did not explain these ethnic differences in prevalence of both depressive and anxiety symptoms.

Since an explanation for the higher prevalence of depressive and anxiety symptoms in immigrant versus native patients was not found in patient characteristics, it was suggested that an explanation may be found in the migration process. In chapter 4, we examined whether acculturation (adaptation of an individual to a new cultural context) was associated with depressive and anxiety symptoms in 249 immigrant chronic dialysis patients. The acculturation aspects “Skills” and “Loss” were significantly associated with more depressive and anxiety symptoms, and thus may partly explain the high prevalence.
of depressive and anxiety symptoms in immigrant patients.

It has been shown that religious struggle (negative religious coping) is associated with more psychological distress in chronic dialysis patients. Therefore, we proposed that religious struggle could also contribute to the higher prevalence of depressive and anxiety symptoms in immigrant patients compared to native patients (chapter 5). Secularization in Europe progresses, but most immigrants are still religious (e.g. Islamic, Hinduism). In both native and immigrant chronic dialysis patients we found significant associations between negative religious coping and depressive and anxiety symptoms. These associations were slightly stronger in immigrant compared to native patients regarding depressive symptoms, and vice versa for associations with anxiety symptoms. So similar impact of religious struggle on depressive and anxiety symptoms was found for both native and immigrant chronic dialysis patients.

Unhealthy versus healthy migrant effect

In both the general hospital setting and more specific in chronic dialysis patients a higher presence of depressive and anxiety symptoms was found in immigrant compared to native patients. Multiple studies in the general population in Europe also found a higher prevalence of both depressive and anxiety symptoms in immigrant compared to native individuals\(^1^\)\(\text{–}^6\), with especially a high prevalence in immigrants from outside Europe (Turkish and Moroccan immigrants)\(^4,^6,^7\). These findings not only apply for mood disorders, but also for psychotic disorders like schizophrenia\(^8\). Remarkably, we found a comparable or even lower prevalence of psychological distress in second generation immigrant patients compared to native patients in the hospital setting. This was also found in other studies in the general population\(^4\) and suggests that migration stress has a significant role in the high prevalence of depressive and anxiety symptoms especially in first generation immigrants.

The results found in European studies are contrary to results from studies in North-America, where lower prevalence rates of mood disorders have been found in immigrants compared to native-born\(^9^\)\(\text{–}^{15}\). This US finding is called the healthy migrant effect or immigrant paradox. This model assumes selection in the country of birth, therefore foreign-born individuals with good mental health are more likely to immigrate than individuals with a poor mental health status\(^1^6\). As a result, these immigrants have a lower risk of psychiatric morbidity, even lower than native-born Americans. This “healthy migrant effect” model not only applies to the mental health of immigrants in the US, but also to physical health. With regard to physical health, also in Europe there are indications of a healthy migrant effect in first generation immigrants\(^2\), but this superior physical health is not protective for their mental health\(^2\).
How could these overall different outcomes in mental health of immigrants between North-America and Europe be explained? Both particular characteristics of the host country and of the immigrant are important. First characteristics of the host country will be discussed. The healthy migrant effect may be particularly applicable to the US because of the geographical location. Due to the greater distance and high costs necessary to travel from major population centers, a relatively healthy selection of immigrants has been able to reach the US. Subsequently, post-migration conditions in the host country are important, such as opportunities for employment and education, economic conditions, socio-political status, and the health care system. It may be possible that in the US only a selection of well integrated immigrants have access to healthcare and participate in studies. Second, important immigrant characteristics associated with mental health are for example: age of the immigrant, length of stay in the host country, mastering the language of the host country, reason for migration (economic, employment, family etc.) and country of origin. Probably the most important immigrant characteristic responsible for differences in the association of immigrant status and mental health in the US and Europe is the country of origin of the immigrant. The migration history of the US differs from the migration history in Europe and therefore, different immigrant populations can be found in both the US and Europe. However, within Europe per country also different immigrant populations can be found and still a higher overall prevalence of depressive and anxiety symptoms is reported. Nevertheless, especially specific subgroups of immigrants in Europe seem to be responsible for the higher prevalence of depressive and anxiety symptoms (e.g. Turkish and Moroccan immigrants in chapter 2 and Asian immigrants in chapter 3). In the US, also studies in specific subgroups of immigrants (for example Puerto Rican immigrants) have been performed in which also a higher prevalence of depressive symptoms has been found. Thus, it is possible that in most studies within-group variation exists, but due to a lack of power these subgroups are not examined separately. Therefore, more details on different subgroups of immigrants per country are needed and every country should identify their immigrant subgroups at risk.

Finally, there seems to be similarity in the prevalence of depressive and anxiety symptoms in second generation immigrant patients in Europe and the US. Namely, also in the US a comparable prevalence of mood disorders was found for second generation immigrants compared to native Americans. The effect found in first generation immigrants in Europe and the US seems to disappear in the next generation, as these individuals are more familiar with western conceptions of mental health and adapted to western behaviors (e.g. alcohol use, food). Based on these results, the mental healthcare needs of second generation immigrants seem much more comparable to individuals from the host country.

Altogether, no overarching conclusion regarding the effect of immigrant status on mental health can be drawn. The findings differ per host country and per immigrant population in the host country. As migrant populations in western countries are becoming
more heterogeneous, it is important to examine the prevalence of depressive and anxiety symptoms in subgroups of immigrants to be able to identify high risk immigrant subgroups. The prevalence of depressive and anxiety symptoms in second generation immigrant patients resembles the prevalence in native patients.

**The effect of acculturation on depressive and anxiety symptoms**

The paragraph above shows that the association between immigrant status and depressive and anxiety symptoms is not yet understood. It is often suggested that migration-related stress might cause depressive or anxiety symptoms and that good acculturation might lower the prevalence of depressive and anxiety symptoms. Migration-related stress and acculturation cannot be considered separately. Each phase in the migration process has its own migration-related stressors. A rough distinction can be made in pre-migration stressors and post-migration stressors. Pre-migration stressors will be especially present for individuals forced to move instead of individuals moving voluntarily. Examples of pre-migration stressors are civil conflicts or war, sexual abuse, or stay in refugee camps. Post-migration stressors are due to the resettlement in a new society and are for example discrimination, language barrier, separation from family, and drop in socioeconomic status. Acculturation is a measure of adaptation to a new society and a moderating factor in the occurrence of post-migration stress. When examining the association between acculturation and depressive and anxiety symptoms an explanation may be found for the higher prevalence of symptoms found in immigrants.

There is not an uniform definition of acculturation and existing scales are not universally valid and applicable in every setting. There are for example, different immigration policies and attitudes towards immigrants. According to the most used definition, acculturation involves both contact and participation in the new society and maintenance of culture and traditions. The questionnaire specifically developed for the Dutch setting measures acculturation on 5 subscales (“Skills”, “Social integration”, “Traditions”, “Values and norms” and “Loss”). As a result, this questionnaire makes it possible to examine which components of acculturation are associated with mental health. We found in chapter 4 that less skills for living in the new society and feelings of loss were associated with depressive and anxiety symptoms in immigrant chronic dialysis patients. However, we did not find a protective effect of preservation of culture and traditions.

Are these results an explanation for the higher prevalence of depressive and anxiety symptoms in immigrant compared to native chronic dialysis patients? As the above described results show we examined the cross-sectional association between the components of acculturation and depressive and anxiety symptoms. By examining cross-sectional associations no conclusions can be drawn on causality. It is clear that we did not find a protective effect of preservation of culture and traditions on depressive and anxiety symptoms, but what is the clinical relevance of the significant associations
found between skills and loss and depressive and anxiety symptoms? The beta for the association between “Skills” and depressive symptoms was $\hat{\beta} = 0.34$ (CI:0.11-0.58), indicating that a patient scoring 10 points higher on the component “Skills” will score 3.4 points higher on the depression questionnaire (BDI). As the subscale “Skills” ranges from 5-30, a maximum higher score of 8.5 points on the BDI is possible, which ranges from 0-63. For “Loss” the effect is smaller, namely a maximum higher score on the BDI of 5.7 points is possible, while for the association between “Skills” and “Loss” and anxiety symptoms the associations are stronger, respectively a maximum of 12.3 points and 9.9 points higher on the BAI (also ranging from 0-63) can be scored. Assuming that native patients will not score on the acculturation components, the effect of “Skills” and “Loss” seems quite relevant, as a score of $\geq 13$ on the BDI and BAI indicates presence of clinically relevant depressive and anxiety symptoms. Therefore, the higher prevalence of depressive and anxiety symptoms in immigrant chronic dialysis patients is at least partly explained by less skills and feelings of loss, but probably also other factors are involved (e.g. pre-migration stressors, post-migration stressors as discrimination).

The effect of religious coping on depressive and anxiety symptoms

In addition to the stressors related to the migration process, more general factors may also explain the higher prevalence of depressive and anxiety symptoms in immigrant chronic dialysis patients.

Religion can be used to deal and cope with stressors, which is called religious coping$^{27}$. Religious coping can be both supportive, but also struggling (tension and conflict about spiritual issues within oneself)$^{28}$. Negative religious coping or religious struggle was associated with psychological distress and impaired quality of life in chronic dialysis patients$^{29}$, while at the same time, positive religious coping has been shown to improve quality of life$^{29}$.

Western European countries are originally Christian (catholic or protestant), but in the Netherlands and other western European countries secularization progresses, which is in contrast with the US. Immigration brings different religions to the western countries (e.g. Islam) and immigrants are in general more religious as they have the tendency to maintain their religious beliefs and behaviors$^{30}$. Therefore, religious struggle might also partly explain the higher prevalence of depressive and anxiety symptoms in immigrant chronic dialysis patients. However in chapter 5, we found for both native and immigrant patients strong associations between both negative religious coping items and depressive and anxiety symptoms. Also, in both groups no protective effect of positive religious coping. Thus, religious struggle does not seem to explain the higher prevalence of depressive and anxiety symptoms in immigrant patients.

It is remarkable that in the native Dutch patients who showed a very low level of religious behavior (daily prayer in 22% and weekly church attendance in 13% of the patients), strong associations have been found for negative religious coping with
depressive and anxiety symptoms. We expected that in the secularized climate of the Netherlands, religiousness would be irrelevant for native Dutch patients, but these results challenge this notion. A phrase which could explain this result is: “There are no atheists in foxholes.” This means that an individual in distress searches for solution in religion in the end. It may be possible that for chronic dialysis patients, the stress experienced from the chronic illness leads to more negative religious coping.

**Part B: Inflammation and tryptophan degradation**

**Main findings**

In chapter 6, cross-sectional associations were found between HsCRP and IL-6 and depressive symptoms in a cohort of 490 chronic dialysis patients. The aim of this study was to examine whether these associations could be explained by tryptophan (TRP) degradation along the kynurenine (KYN) pathway. By adjusting the association between HsCRP/IL-6 and depressive symptoms for TRP degradation, we found no evidence that TRP degradation mediated this association. While, the inflammatory markers HsCRP, IL-6 and TNFα were significantly associated with tryptophan degradation and a lower TRP concentration was significantly associated with depressive symptoms.

To understand the direction of the inflammation-depression association and whether long-term associations exist we performed a longitudinal study in 513 chronic dialysis patients in chapter 7. No significant associations were found between inflammatory markers (HsCRP, IL-1b, IL-6, IL-10 and TNFα) at baseline and depressive symptoms at 6 and 12 months follow-up. Also no significant associations were found between depressive symptoms at baseline and inflammatory markers at 6 and 12 months follow-up. As a result, the direction of the inflammation-depression association was not explained.

Finally, we examined whether differences exist in the inflammation-depression and tryptophan-depression association between white and non-white chronic dialysis patients in chapter 8.

The presence of depressive symptoms was significantly higher in 220 non-white patients compared to 270 white patients, namely 51% versus 37%. Stronger associations between inflammatory markers and depressive symptoms were found in non-white patients and TRP levels were only significantly associated with depressive symptoms in non-white patients. So, racial differences in the association between inflammation and depressive symptoms and TRP and depressive symptoms exist. TRP degradation along the KYN pathway did not mediate the association between inflammatory markers and depressive symptoms in both groups.

**Are inflammation and depression associated in chronic dialysis patients?**

A lot of studies in chronic dialysis patients examined cross-sectional associations between
inflammatory markers and depressive symptoms, the results were recently summarized in a review by Taraz et al\textsuperscript{32}. Eleven out of the 23 studies described in this review found significant cross-sectional associations between inflammatory markers and depressive symptoms, mostly for IL-6 or CRP. These studies consisted of both small and larger cohorts and included both hemodialysis and peritoneal dialysis patients. Studies in the present thesis also found cross-sectional associations between inflammatory markers and depressive symptoms. In chapter 6, significant associations between HsCRP and IL-6 and depressive symptoms were found. In chapter 7, at baseline, 6 months and 12 months different associations were found, namely at baseline a significant association between HsCRP and depressive symptoms, at 6 months between HsCRP and IL-1b and depressive symptoms and at 12 months between IL-1b and depressive symptoms. Finally, in chapter 8, only HsCRP was modestly associated with depressive symptoms in white patients, while HsCRP and IL-6 were stronger associated with depressive symptoms in non-white patients. Thus, cross-sectional associations seem to differ per measuring point and per subgroup analyzed.

In this thesis, no longitudinal associations between inflammatory markers and depressive symptoms were found (chapter 7). No other studies in chronic dialysis patients examined longitudinal associations between inflammation and depressive symptoms, but multiple studies in the general population did\textsuperscript{33-41}. All general population studies found in contrast to our study, significant longitudinal associations in one of both directions, but also one study found a bidirectional association\textsuperscript{38}.

Why are cross-sectional associations uncertain and are inflammatory markers not longitudinally associated with depressive symptoms in the chronic dialysis patient group? First, a possible explanation is that inflammation-depression associations are more pronounced in certain subgroups, and therefore, effect sizes may be too small in some studies reviewed by Taraz et al\textsuperscript{32}. For example, we found stronger associations in non-white chronic dialysis patients compared to white patients. All other cross-sectional studies did not examine racial differences and mostly did not describe the racial composition of their cohorts. Also regarding longitudinal associations in the general population, it was found that depressive symptoms were more closely linked to inflammation in black participants\textsuperscript{34}. Other subgroups that have been examined are hemodialysis/peritoneal dialysis patients, because the filtering of cytokines may differ for both dialysis methods. We found comparable results in the hemodialysis group compared to the total group, but the peritoneal dialysis patient group was too small to draw conclusions on. However, Taraz et al reviewed both studies including only hemodialysis or only peritoneal dialysis patients, without a clear difference in outcome\textsuperscript{32}. Furthermore, studies in the general population examined the inflammation-depression association in older aged subjects or separate for women or men. Some studies found that only among men inflammation was associated with depression\textsuperscript{42,43}. In chronic dialysis patients it is not specifically explored whether differences exist for age or gender, but after adjustment for age and
gender, associations in our study did not change. Second, the method of measuring depression might be responsible for the differing results. In community and clinical samples the effect sizes were halved when using depressive symptoms assessed with a self-report questionnaire as outcome compared to depressive disorder assessed with a structured interview. However, 3 of the studies reviewed by Taraz et al used a clinical diagnosis of depression as outcome and 2 of these studies did not find significant associations. Therefore, a uniform method of measuring depression does not seem to be responsible for the differing results. Third, another possible explanation is that only certain subtypes of depression are associated with inflammation. As depression is a heterogeneous condition it is possible that inflammation is related to some, but not all types of depression. It has been found in the general population, that inflammation is more specific for the atypical depression subtype, instead of melancholic depression. Another common subdivision of depression is into somatic and cognitive symptoms of depression. Especially the somatic symptoms of depression were associated with inflammation. Whether specific subtypes of depression are more strongly associated with inflammation in chronic dialysis patients has not been examined yet.

Altogether, the cross-sectional associations we found between inflammatory markers and depressive symptoms are somewhat inconsistent, which is in line with other studies in chronic dialysis patients. Furthermore, we found no evidence for longitudinal associations. Therefore, these results are more supportive for an associative rather than a causal relationship between inflammation and depressive symptoms in chronic dialysis patients.

The role of tryptophan degradation

Another way to examine causality is by examining the role of a possible pathogenetic pathway. TRP degradation along the KYN pathway has been mentioned as a possible explanation for the cross-sectional associations between inflammatory markers and depressive symptoms in chronic dialysis patients. The underlying theory is that inflammatory markers activate the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades TRP into its degradation product KYN. Both a low concentration of TRP and higher concentrations of degradation products of KYN (i.a. 3-OH-KYN) may be responsible for depressive symptoms. TRP degradation can be measured by calculating the KYN/TRP ratio.

In chapter 6, we examined the role of TRP degradation by adjusting the association between inflammatory markers and depressive symptoms for the KYN/TRP ratio, but we did not find the expected role of TRP degradation. However, we did find two relevant associations. First, inflammatory markers were as expected significantly associated with a higher KYN/TRP ratio, indicating that the activation of IDO is induced by inflammatory markers. This was also found in another study among CKD and chronic dialysis patients. Second, we also found a significant association between a lower concentration of TRP
and more depressive symptoms. Also in non-physically compromised patients low TRP concentrations were found in patients with depressive disorders\textsuperscript{51}. This points to a comparable TRP involvement in depressive symptoms in both chronic dialysis patients and healthy individuals.

Despite the finding of these two associations, why does TRP degradation along the KYN pathway not seem to be responsible for the association between inflammation and depression?

It is clear that IDO activity is much higher in this chronic dialysis patient group compared to healthy individuals\textsuperscript{52} and this is most likely caused by the high concentration of inflammatory markers. As a result the TRP concentration is significantly lower in these chronic dialysis patients and the KYN concentration higher compared to the general population. However, a low TRP and high KYN concentration do not seem to be major contributors to the development of depressive symptoms in this patient group. It is remarkable that the mean concentrations of KYN and 3-OH-KYN were lower in depressed patients compared to non-depressed patients and the KYN/TRP ratio was equal in both groups. The association between TRP and depressive symptoms was significant, but rather small ($\beta$ -0.1 (CI: -0.2 - 0.01)) and after adjustment for socio-demographics, lifestyle factors and medical variables the association lost significance. Therefore, TRP seems to have a small contribution in the onset of depressive symptoms, but other factors are likely to play a more important role.

In chapter 8 we examined the association between TRP and depressive symptoms in both white and non-white chronic dialysis patients. In the white patients no association between TRP and depressive symptoms was found, while in the non-white patients a relatively strong association was found ($\beta$ -0.3 (CI: -0.4 - 0.1). Thus, the contribution of TRP on depressive symptoms in non-white patients is stronger. Therefore, we also examined the role of TRP degradation in the association between inflammatory markers and depressive symptoms in both groups, but also no mediating role was found in the non-white patients.

These results suggest that TRP degradation along the KYN pathway is not the link between inflammatory markers and depressive symptoms in chronic dialysis patients. A study in individuals with a major depressive disorder (MDD) in the Dutch general population also found no role for TRP degradation in the association between inflammatory markers and MDD\textsuperscript{53}. This study used the same method, by adjusting the association between inflammatory markers and MDD for the KYN/TRP ratio. Therefore, the evidence which came from theory and animal studies appears not to be explanatory in vivo. As our longitudinal study in chapter 7 provided no evidence for a causal relationship between inflammation and depression, the question is whether other pathways (e.g. hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA)-axis) may explain the cross-sectional association.
Racial differences in biochemical parameters and depressive symptoms

Most studies examining differences in the prevalence of depressive symptoms in immigrant versus native patients focus on socio-demographic factors. In addition to socio-demographic factors, we focused in Part A on acculturation and religion as explanations for the higher prevalence of depressive symptoms in immigrant chronic dialysis patients. Thus far, biochemical parameters have not been taken into account. In chapter 8, we chose to examine racial differences (white versus non-white) instead of using immigrant status in the association between inflammatory markers and depressive symptoms and TRP and depressive symptoms, as race refers to physical characteristics. As discussed above, racial differences were found in both the association between inflammatory markers and depressive symptoms and TRP and depressive symptoms.

Do these racial differences also explain the higher prevalence of depressive symptoms in the immigrant chronic dialysis patients? As immigrant patients can be found in both the white and non-white patient group, race and immigrant status cannot be considered the same. However, the proportion of immigrant patients in the white chronic dialysis patient group is very small (10.7%). No native patients were found in the non-white chronic dialysis patient group. Therefore, the white and non-white patient group are overall quite comparable to the native and immigrant patient group respectively. Thus, these results indicate that racial differences found in chapter 8 also partly explain the higher prevalence of depressive symptoms in the immigrant compared to native chronic dialysis patients.

Immigrant status, ethnicity and race

In this section an overview of the concept and definitions of immigrant status, ethnicity and race will be provided as a theoretical framework belonging to chapters 2-5 and 8. The general definition of ethnicity is: “The social group a person belongs to as a result of a mix of cultural factors including language, diet, religion, ancestry, and physical features traditionally associated with race.” The concept of ethnicity is overlapping with the concept of race and both concepts are often used synonymously. Race is defined as: “The group a person belongs to as a result of a mix of physical features such as skin color and hair texture, which reflect ancestry and geographical origins.”

There is no consensus about the assessment of ethnicity and race in research and multiple classifications can be found. In North-America mostly self-perceived ethnicity is used, while in the Netherlands country of birth of the individual and of their parents is used as an indicator of ethnicity. Furthermore, in the Netherlands and other western European countries a different ethnic history and composition can be found compared to the US, which is due to a different migration history. Both the use of different classifications in publications and different ethnic compositions in countries makes the
comparison of studies, especially internationally, difficult54.

Immigrant status differs from ethnicity and race, but also includes elements of both concepts. Immigrant status is more specifically defined and focuses on the migration history of an individual (by measuring country of birth of an individual and their parents). Due to continuing migration, doctors will be confronted with increasing amounts of non-native (immigrant) patients. Therefore, we chose to examine immigrant status in Part A of this thesis. The classification of immigrant and native patients in all chapters was uniform, according to the immigrant definition of Statistics Netherlands56. However, the subdivision of the immigrant patient group differs per chapter depending on the study population and research question. In chapter 2, we were able to make a subdivision according to country of origin (Turkey, Morocco, Indonesia, Surinam and other), due to the large representation of immigrants from these countries. However, in the DIVERS study patients from 38 different countries were participating and numbers were smaller, for example 5 patients from India, 15 patients from Turkey and 17 from Morocco. Therefore, we decided to use the United Nations classification, dividing countries by major area or region of the world57. In chapter 4, immigrant patients were divided in 5 regions of origin: Europe, Sub-Saharan Africa, Northern Africa/Western Asia, Southern Asia/South Eastern Asia and South America/Caribbean. However, in the US, patients are mostly divided in Caucasian, Asian and Black (African-American) patients or white and black patients58. Multiple studies in the US examined racial differences in the prevalence of depression in CKD patients59-62. To be able to compare our results internationally we decided to make a division in 3 regions of origin in chapter 3: Europe, Asia and African-South American, which is more comparable to the division in Caucasian, Asian and Black. In chapter 8 we examined biochemical markers (inflammatory markers and tryptophan) and therefore chose to examine racial differences instead of immigrant status. Patients were divided in white and non-white patients, again to be able to compare the results with international publications63,64, but we also made a subdivision in the above mentioned 5 regions of origin.

These differing subdivisions of immigrant patients results in less uniformity throughout this thesis. When patients are divided in only two (white/non-white) or three (European, Asian, African-South American) groups more heterogeneity in a group is created. As a result, it is possible that countries with different cultures end up in one group. We have specifically chosen to mention the region of origin according to the United Nation classification, since these regions of origin are based on international agreement57. The discussion regarding the classification of ethnicity and race has not been solved in the last decades54. Purpose and context are decisive for the way the concepts of ethnicity and race are applied in studies54. A division in race can be made when biological factors are examined and in ethnicity or immigrant status when examining cultural factors. Most important is that authors clearly explain what is meant with race or ethnicity in their publications54. In general, it is not advisable to divide individuals in large groups,
rather choose for the classification in for example the 5 different regions of origin or per country.

**Implications and recommendations for further research**

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

The prevalence of depressive and anxiety symptoms in medically ill and in chronic dialysis patients is high. This prevalence appears to be higher in first generation immigrant patients compared to native and second generation immigrant patients. In the Dutch setting especially Turkish and Moroccan patients are vulnerable. However, the most vulnerable patient groups differ per host country and each country should identify their immigrant patient groups at risk. It is important that clinicians are aware of this higher prevalence of depressive and anxiety symptoms in the immigrant patient group, so the presence of these symptoms will not be missed. Certain aspects of acculturation (less skills and feelings of loss) could increase the risk of developing depressive and anxiety symptoms in the immigrant chronic dialysis patients. Therefore, the improvement of these acculturation aspects may lead to less depressive symptoms. Assessment of the acculturation status of immigrant chronic dialysis patients may be used to identify immigrant patients at risk. Standard screening of depressive and anxiety symptoms in chronic dialysis patients (using a questionnaire) should be implemented and subsequently appropriate care should be offered. It is remarkable, that negative religious coping is strongly associated with more depressive and anxiety symptoms in both native and immigrant chronic dialysis patients. Thus, in a secularized climate as the Netherlands negative religious coping is still relevant. However, it is not clear whether this struggle could benefit from recognition by clinicians or should be treated.

More research is needed in immigrant chronic dialysis patients to identify other risk factors (e.g. discrimination) that may explain the higher prevalence of depressive and anxiety symptoms. It would be interesting to examine the effect of depressive and anxiety symptoms, acculturation and religion on morbidity and mortality in native and immigrant chronic dialysis patients. Furthermore, it is important to focus on an effective treatment for depressive and anxiety symptoms in chronic dialysis patients and also an adapted treatment for the immigrant chronic dialysis patients.

**Part B: Inflammation and tryptophan degradation**

In addition to patient characteristics and cultural factors responsible for the development of depressive and anxiety symptoms in chronic dialysis patients, also biochemical parameters may be involved in the development of depressive symptoms. The cross-sectional association between inflammatory markers and depressive symptoms appears to be uncertain, it differs per measuring point and per racial subgroup. Namely,
inflammatory markers were stronger associated with depressive symptoms in non-white chronic dialysis patients. The association between TRP and depressive symptoms was only found in non-white chronic dialysis patients. These racial differences may also partly explain the higher prevalence of depressive symptoms in immigrant chronic dialysis patients. It is advisable to examine biochemical parameters on multiple measuring points and in case of a racially mixed cohort to divide in racial subgroups. These results may also reflect the heterogeneity of depression, whereby only certain subtypes of depression are associated with inflammation. Despite the chronic inflammatory status of dialysis patients, this does not seem to cause depressive symptoms on the long-term. Also, depressive symptoms did not cause inflammation at 6 and 12 months follow-up. Therefore, whether a causal relationship exists between inflammation and depressive symptoms in chronic dialysis patients is still not clear.

Studies are needed to explore whether specific subtypes of depression are associated with inflammation both cross-sectionally and longitudinal in chronic dialysis patients. Also, the association between inflammatory markers and morbidity and mortality should be examined. Furthermore, to examine causality in the association between TRP and depressive symptoms exploration of longitudinal associations would be interesting.

Main conclusion
The presence of depressive and anxiety symptoms is high in medically ill and in chronic dialysis patients, with an especially high presence in first generation immigrant patients. Some aspects of acculturation (less skills to function in the new society and feelings of loss) appear to contribute to the higher presence in immigrant patients. While negative religious coping was strongly associated with depressive and anxiety symptoms in both native and immigrant patients.

Cross-sectional associations between inflammatory markers and depressive symptoms in chronic dialysis patients are variably found. Racial differences have been found, with stronger associations between both inflammatory markers and TRP with depressive symptoms in non-white chronic dialysis patients. These racial differences may also partly explain the higher prevalence of depressive symptoms in immigrant patients. No, longitudinal associations between inflammatory markers and depressive symptoms were found and no mediating role of TRP degradation in the cross-sectional association between inflammatory makers and depressive symptoms.
REFERENCES


