The disparity of renal disease in immigrants in Europe:

Why - what are the research gaps - and what to do?

Lea Zoe Landolt
Switzerland

Master in International Health

Declaration

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By

Lea Zoe Landolt, Switzerland

Declaration:

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The thesis *"The disparity of renal disease in immigrants in Europe: Why - what are the research gaps - and what to do?"* is my own work.

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Abstract

Chronic kidney disease (CKD), defined by a reduced kidney function, leads over time to conditions like hypertension and oedema. CKD can progress and require renal replacement therapy (RRT) i.e. dialysis and transplantation. CKD has a high morbidity and mortality and its prevalence is on the rise worldwide.

The aims of this thesis were to describe the epidemiology of CKD and RRT in immigrants in Europe, to discuss underlying mechanisms, and to detect gaps of existing research and knowledge.

Based on systematically reviewing the literature, studies indicate a higher prevalence and progression of CKD, as well as a superior survival of immigrants on dialysis, as compared to the majority in Europe.

Reasons for this disparity are insufficiently studied. Underlying mechanisms are probably multifactorial and may arise from a combination of genetic risk variants, higher prevalence of diabetes, hypertension and obesity, higher risk of low birth weight (LBW), and preeclampsia in some immigrant subpopulations, as well as an interplay of social determinants like low socioeconomic status and education, cultural shaped aspects, and possibly impaired access to health care services, particularly to primary care. LBW is more common in socially deprived populations and may therefore play a relevant role in linking social disadvantage to CKD.

In conclusion, CKD represents an important burden of disease in immigrants in Europe and more research is needed to understand the underlying mechanisms. Findings could help to improve the health state of the whole populations at risk, and help to advance the evidence to appropriate policymaking.

List of tables and figures

Abbreviations

ACEI	Angiotensin-converting-enzyme inhibitors
BP	Blood pressure
CKD	Chronic kidney disease
DM	Diabetes mellitus
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
GBD	Global burden of disease studies
GFR	Glomerular filtration rate
eGFR	estimated Glomerular filtration rate
HD	Haemodialysis
HIC	High-income countries
HR	Hazard ratio
LBW	Low birth weight
LMIC	Low and middle-income country
NCD	Non-communicable disease
NP	Nephropathy
NL	The Netherlands
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PE	Preeclampsia
PD	Peritoneal dialysis
RODAM	Research on obesity and diabetes among African Migrants
RR	Relative risk
RRT	Renal replacement therapy
SA	South Asia, or South Asian (s)
SDH	Social determinants of health
SES	Socioeconomic status
SSA	Sub-Saharan Africa, or sub-Saharan African (s)
UK	The United Kingdom
UKRR	UK Renal Registry
US	The United States of America

Introduction

After working a couple of years as a physician in Switzerland, I took part in the "Netherlands Course on Global Health and Tropical Medicine" (NTC) in 2013. I was very intrigued by understanding how social, "non-medical" aspects of life, such as education, income or culture, affect health of people, and that this not only concerns communicable, but also non-communicable diseases. I was also surprised by the health disparities within Europe.

Later, as a part of my academic training, I took a PhD in biomedicine, where I was involved in analysing molecular mechanisms of renal disease by assessing renal tissue RNA sequencing profiles. We concluded, that one of the genes of interest could be a potential treatment target for chronic kidney disease in the future.

During this time, I still pursued my interest for international health by taking advanced courses, like "Globalisation and health", "Cultural psychopathology", and "Strategies to control communicable and non-communicable diseases".

After finishing the PhD, I wished to "close the circle", by not only having analysed molecular determinants, but also by assessing and discussing overall determinants of renal disease - this time from an international health perspective.

The European population only grows owing to migration, and migration has been an important topic in European politics in the past years. I have also noticed that some immigrants I met during my clinical work are confronted with serious health issues. Are immigrants sicker than the majority - and if so, why? Such questions lead me to the aim to discuss if, and why renal disease is "different" in immigrants in Europe.

With this thesis, I hope to achieve several goals. On one hand, the thesis reflects the final assignment of the Master in International Health course, and I would like to apply what I learned from and since the NTC to reflect my development. Furthermore, I wish to deepen my knowledge on renal disease in a broad sense, as I would like to continue working on this topic in the future. Finally, I wish to address renal health in immigrants in Europe, to raise awareness on renal disease, to promote attention on health disparity, and in particular on immigrant´s health.

1 Background

1.1 Why do we have kidneys?

The kidney is a paired organ situated on each side of a person's spine. The kidneys comprise more than 1 million nephrons each, responsible of filtering around 180 litres of "ultrafiltrate" out of the blood every day. The primary function of the kidneys consists into secretion and reabsorption of salts such as sodium and potassium, balancing the water volume and the acid-base household according to the body´s need. The kidneys are also involved in blood pressure (BP) regulation; they activate vitamin D and produce erythropoietin, promoting bone metabolism and erythrocyte production. The kidney's function is measured by the "glomerular filtration rate" (GFR), which describes how much ultrafiltrate is filtered out of the blood per time unit. "Renal disease" and "Kidney disease" are synonyms.

1.2 Chronic kidney disease

1.2.1 Definition

Chronic kidney disease (CKD) can be defined as a reduced renal function with a GFR below $60ml/min/1.73m^2$ for more than three months. CKD is mostly classified by GFR (Table 1), and can progress to end-stage renal disease (ESRD), which requires renal replacement therapy (RRT), defined as chronic haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation. The transplanted kidney is also called "allograft" (1).

GFR categories	CKD stage
30 - 60 ml/min	3
15 - 29 ml/min	4
<15 ml/min	5
ESRD	CKD requiring RRT

Table 1: Classification of chronic kidney disease (CKD) based on glomerular filtration rate (GFR). End-stage renal disease (ESRD) is defined as CKD requiring renal replacement therapy (RRT) (1).

1.2.2 Epidemiology and risk factor for CKD

CKD is very common and has a global prevalence of 11% to 13% (2, 3) (Figure 1). In Europe, main causes of ESRD are diabetes, hypertension, glomerulonephritis and genetic diseases, such as polycystic renal diseases. Other causes of ESRD are infections like chronic pyelonephritis, tubulointerstitial nephritis, vasculits, and congenital anomalies. Low birth weight (LBW) is linked to an increased ESRD risk later in life (4). Preeclampsia (PE), a gestational complication characterised by high BP and proteinuria, is also associated with more ESRD in the mother later in life (5). Causes of ESRD differ geographically: In the US for example, the most common cause is diabetes, whereas in Norway it is most commonly hypertension (6-8). In China and sub-Saharan African (SSA) countries, ESRD caused by glomerulonephritis prevails (9, 10) (Figure 2).
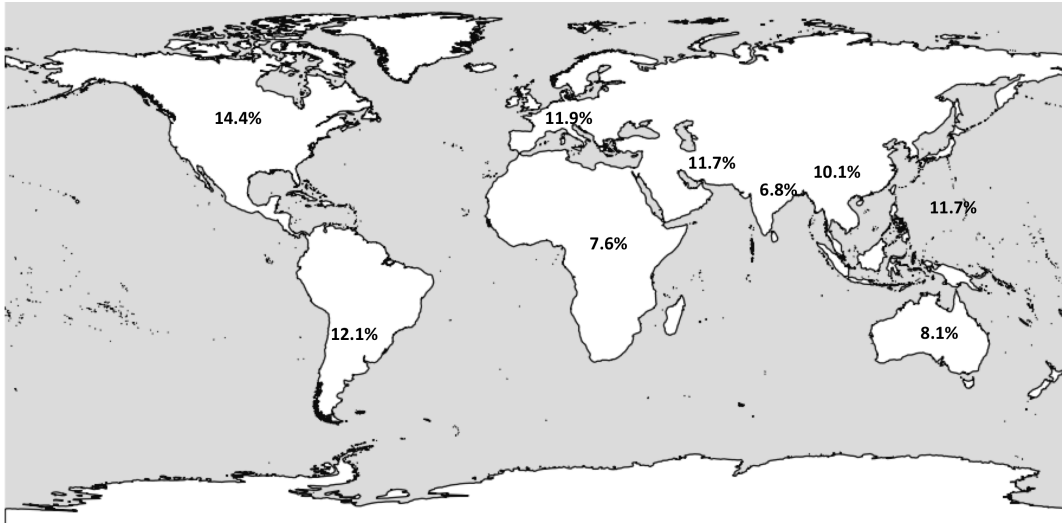
Figure 1: Global prevalence of CKD stage 3-5. (Map generated by SimpleMappr, http://simplemappr.net. Prevalence data extracted from (2)).

1.2.3 Clinical characteristics and treatment of CKD

In early stages, CKD is often asymptomatic. Advanced CKD is characterised by increasing hypertension, electrolyte abnormalities, acidosis, bone disease, retention of toxic metabolites, anaemia and malnutrition (6). CKD is irreversible and often progressive. Hypertension, hyperglycaemia, and proteinuria, as well as age, male gender, smoking and comorbidities promote progression (6, 11). Management of CKD includes treatment of the cause, of symptoms and complications, and of risk factors for progression. Proteinuria can be reduced by renin-angiotensin-aldosterone-system inhibition, such as angiotensin-converting-enzyme inhibitors (ACEI) (1).
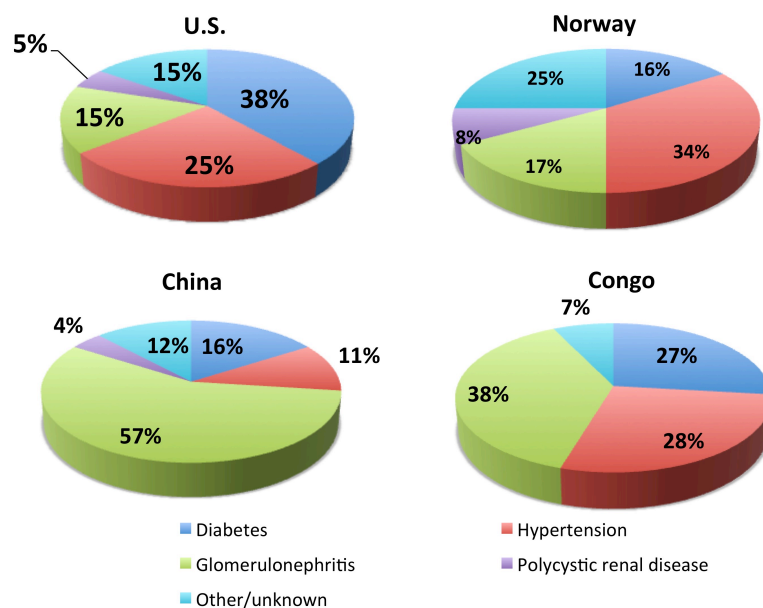
Figure 2: Causes of ESRD in the U.S., Norway, China and Congo (7-10)

1.2.4   The burden of CKD

Morbidity is distinctly increased in patients with CKD and mortality increases exponentially along progressing CKD. Morbidity and mortality is driven by infections, cancer, and particularly hastened arteriosclerosis leading to stroke or heart attack, already in early stages (12, 13). Global mortality due to CKD is probably underestimated, as cardiovascular disease, the most common cause of death, is often not linked to CKD (13).

Quality of life is severely impaired in patients with advanced CKD and has been compared to patients after stroke or with metastatic cancer (14).

Treatment of CKD leads to high costs. It is estimated, that in high-income countries (HIC), around 2-3% of health service related expenditure is due to RRT - while the prevalence of ESRD is around 0.2% (13). The expenditures of early CKD are suggested to be even higher. In countries with low resources or without universal health care coverage, ESRD can impoverish families, or be unaffordable. Additionally, patients and families often have to travel to receive specialised care. Transplantation is the best option when it comes to survival and costs (3, 13).

Despite the high burden of CKD globally, the awareness of CKD is low; In the US, only around 6-8% of a high-risk population were aware of CKD, despite higher disease prevalence (3, 15).

1.3   Migration to Europe

1.3.1   Definitions

There is no internationally accepted definition of "immigrant". According to the International Organization for Migration (IOM), an immigrant can be defined as a person who resides away from his origin and place of birth. Earlier, immigrants were defined as people living abroad more than one year. Nowadays, these immigrants are characterized as long-term immigrants. All individuals traveling or staying temporarily abroad due to holiday, pilgrimage or for example medical treatment, are excluded, and do not count as immigrants.

An immigrant can be "internal", when migration takes place within the home country, or "international", when the country border is crossed. In the context of this thesis, "immigrant" is the term used for "international" immigrants. "Immigrant" is a broad term and is used irrespective of the reason for migration - including refugees, asylum seekers, working migrants, family reunification and education migrants. Undocumented persons are also immigrants, with a different legal status (16, 17). In the light of this thesis, migrants are mostly grouped according to the country or region of origin, such as "South Asian" (SA) for individuals originating from the Indian subcontinent, or sub-Saharan Africans (SSA) for individuals from all SSA countries. Other possible categories are the cause of migration, like "forced", or "voluntary" migration.

Children of immigrants born in the host country, are often described as "second generation immigrants" (18). Latter is per definition an incorrect term, as these children have not immigrated themselves. However, individuals with immigrant background, such as children from

immigrant, may have been influenced by the migration history of their parents and display particular behaviours, social patterns and health related risk factors.

The word <u>ethnicity</u> derives from the ancient Greek word ἔθνος, which means "the people", in the sense of "nation" or "tribe". Ethnicity can be determined as a group, or community with a common geographic origin, history and culture - including language, religion and traditions. All human belong to an ethnic group. However, there is no agreement on how to define "ethnic groups" in the context of health research, this term is imprecise and difficult to measure objectively. A common means of declaring ethnic belonging, is self-reporting, though ethnicity is dynamic and can change during life (19).

In the context of this thesis, the term "ethnic group" is solely used in the context of studies from UK, where "ethnic groups" depict non-White populations. Most are immigrants - even though the term is used irrespective of nationality or immigrant status.

1.3.2   Immigrants in Europe

Migration is a phenomenon that dates back to the beginnings of human history. Migrants leave their countries due to political, economic, social or environmental reasons. They leave their home, culture and sometimes also family in the hope to find better living conditions, and in the case of refugees, security in another country. In 2015, around 244 million individuals, making 3.3% of the global population, were international migrants, even more being internal migrants (20). The country with the most immigrants is USA, with around 50 million, contributing to more than 14% of the population. However, a higher prevalence of immigrants are seen e.g. in Australia and Switzerland with nearly 30% of the population being immigrants.

In 2015, a third of international immigrants (around 75 millions) resided in Europe, and nowadays, the European population actually grows barely owing to immigration (21). More than half of these immigrants are non-European; of these, most are born in low and middle-income countries (LMIC) in Asia or in Africa (20). Most immigrants live in Germany, followed by UK, Italy, France and Spain (22).

Immigration to Europe has occurred in different phases. The largest migration phase occurred around World War II, when around 14 million people migrated from Eastern to Western European countries. After World War II and the early 70s, the thriving economy attracted labour migrants in particular from colonies and from Southern Europe. In the 70s, migration began to be restricted, and most immigration was owing to family reunification. Later, after the fall of the Soviet Union and Yugoslavia, and the opening of the borders, immigration to Europe experienced another peak (23).

In 2015, an (ongoing) "European migrant crisis" was declared, when an increase in immigrant influx with more than 1 million migrants was seen, mainly from Syria, Afghanistan, Iraq, and also African countries like Eritrea; many seeking asylum (24, 25).

Overall, Europe benefits from immigration, who contribute crucially to the growing economics of European countries, and also to social services; A substantial share of teachers, childcare assistants, health care professionals and other personnel working in health care service like hospitals or nursing homes, are immigrants (17).

But what about immigrant´s health, how does migration influence health, and how about renal diseases in immigrants in Europe?

2 Rationale, objectives and methods

2.1 Problem statement and justification

2.1.1 CKD is a global public health issue and prevalence is expected to rise world wide

The rationale of this thesis is that CKD is a very common non-communicable disease (NCD) with a high burden due to high prevalence, morbidity, mortality and costs (3, 13).

Years of life lost (YLL) due to CKD have increased worldwide by over 50% from 1990 to 2013 and the prevalence of CKD is estimated to further grow - particularly due to the rise of obesity and diabetes (26, 27). More than 400 million people had diabetes in 2015 and these numbers are expected to escalate to 640 million by 2050 (28).

The burden of CKD is particularly high in LMIC, where CKD has reached the top ten for YLL in many countries (26, 29). This is probably mostly linked to globalisation, rapid urbanisation and epidemiologic transition with increased prevalence of NCD such as diabetes, hypertension and obesity. Additionally, low access to health care and RRT further aggravates the burden. Nowadays it is suggested, that up to three quarters of individuals with diabetes reside in LMIC (28, 30).

2.1.2 Europe is increasingly multi-national

In the past century, Europe has experienced different phases of immigration, and nowadays 75 million people in Europe are immigrants. The mix of different origins makes most European countries multi-national and multi-cultural (20). Immigration to Europe is increasing (18, 22).

2.1.3 Migration is a determinant of health

Migration itself is a determinant of health and substantially influences the health state of individuals in a complex and dynamic manner. Migration actually intersects with all determinants of health, as they are widely known and described by Dahlgren and Whitehead (17, 18, 31).

Health of immigrants is shaped by the health state and determinants on different time points that can be categorized into the "pre-migration", the "transit" phase, and later the arrival at the "host country" (Figure 3). In the pre-migration phase in the country of origin, the general socioeconomic, political, living and working conditions, health care services, social structures and the epidemiology of disease influence the immigrant´s health at the base. During the transit phase, circumstances and duration of the travel, access to health care services and continuity of treatment may affect the migrant´s health. Arriving at the destination, the host country, health depends on factors such as the legal circumstances and policies, on new living and working condition, on the exposure to a different epidemiology of diseases, on lifestyle change, language skills, and access to the health care service. "Stress" and "acculturation" are other factors that play a role in an individual's wellbeing and health. The migrant's health is also influenced by the

reason for migration ("push" factors at the place of origin and "pull" factors at the destination). All phases can also be traumatic and include discrimination, abuse or violence (17, 18, 32).
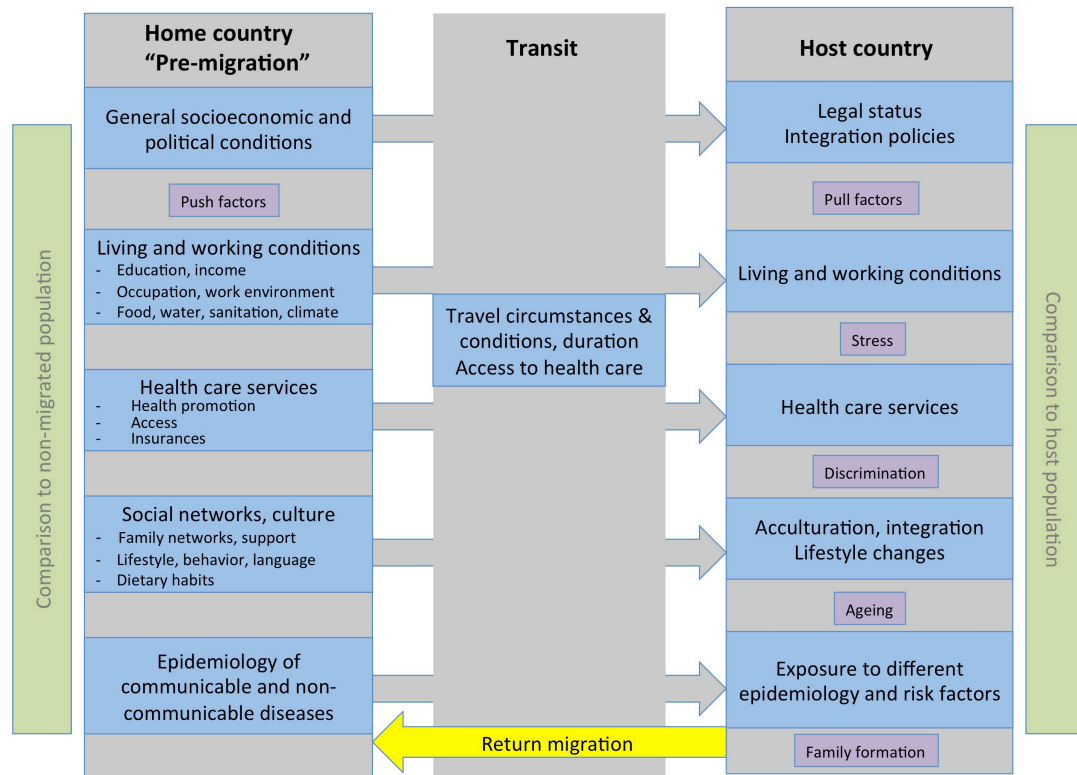
Figure 3: Migration as a determinant of health. This figure depicts all determinants affected by migration and influencing the health of individuals in their home country ("pre-migration" phase), during migration ("transit") and as immigrants arrive at the destination ("host country"). Figure adapted from Abubakar et al., and Kumar and Diaz et al. (17, 32).

2.1.4   Immigrant´s health

Migration from difficult or precarious conditions may improve living circumstances, reduce risk factors, and is thus not necessarily linked to worse health. In fact, generally, immigrants are healthier than the majority (17). A metaanalysis points towards an overall lower mortality in immigrants in HIC, as compared to the host population, in many disease categories, except for infections and violence related causes of death (33). Lower mortality was also seen to be irrespective of the cause for migration; refugees had fewer stroke than the majority in Denmark, and a survival benefit as compared to the general population in Norway (34, 35). Cancer, in particular the entities not related to infections like breast or lung cancer, are distinctly rarer in immigrants and thus mortality due to malignancy is lower than the general population (36). However, in the "ULC-Lancet commission on Migration and Health" publication it is stated, that infections and NCD, like diabetes and hypertension, as well as pregnancy and birth related complications are more common in immigrants (17).

2.1.5 Social disadvantage negatively influences renal health

Socially disadvantaged people, e.g. with a low socioeconomic status (SES), education and low social support, are known to have a higher prevalence of CKD (37). Additionally, individuals with already diagnosed CKD with low SES and low education are known to more often require RRT and have a higher cardiovascular risk compared to patients with high income and education (38).

2.1.6 Immigrants may be more socially disadvantaged than the majority

Immigrants may be more disadvantaged, for example due to a shift in the SES upon migration, acculturation issues including language problems, barriers to access to health care services and also due to discrimination. This may lead to a health disparity as compared to the majority (17).

2.1.7 Justification

The interplay of CKD related conditions, like the higher occurrence of diabetes and hypertension, pregnancy complications and social disadvantage, may point towards a higher prevalence of CKD and worse outcome in immigrants in Europe, as compared to the majority. The outcome after transplantation may be worse due to more infections. Mortality is generally increased in CKD, though it is unknown if that is similar in immigrants as compared to the host population.

There is a low awareness for CKD, and health disparity generally, and immigrants may have different health related issues and needs as compared to the majority.

Ministries of health and public health policy makers in Europe need to be aware of a possibly different epidemiology of CKD in immigrants in Europe. This may help to advance the evidence to appropriate policymaking.

2.2 Hypotheses

The hypotheses of this thesis were that:

1. There is a health disparity in renal disease: Some immigrant subgroups have a different epidemiology of CKD and outcome of RRT as compared to the majority in Europe.
2. Reasons for this health disparity are linked to both biological factors and social determinants of health, and also to pregnancy complications like LBW and PE.

2.3 Objectives

The overall objective of this thesis was to discuss what kind of research and measures are needed to improve knowledge on, and address the renal health disparity of CKD and RRT in immigrants in Europe.

Therefore, the specific objectives of this thesis were:

1. To describe the epidemiology of CKD and RRT in immigrants;
2. To discuss determinants and underlying mechanisms involved in CKD and RRT in immigrants;
3. And to find gaps of the existing research on CKD and RRT in immigrants in Europe.

2.4 Methods

2.4.1 Search strategy

To describe the epidemiology of CKD and RRT in immigrants in Europe, a systematic literature review was conducted using the databases Pubmed and Embase. Snowballing (analysis of reference lists to find other articles of interests) was performed on the articles retrieved from the search. The PRISMA statements were used to report the studies (39). The search terms are listed in the text box below.

Pubmed: ((europe[MeSH Terms]) AND (((("ethnic groups"[MeSH Terms]) OR ("emigration and immigration"[MeSH Terms])) OR ("emigrants and immigrants"[MeSH Terms])) OR "race factors"[MeSH Terms]) AND ((renal insufficiency, chronic[MeSH Terms]) OR "renal replacement therapy"[MeSH Terms])

Embase: (Exp immigrant/ OR Exp immigration/ OR Exp Ethnic group/ OR Exp Race) AND (Exp kidney disease OR Exp Renal replacement therapy) AND Exp Europe

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Text box 1: Search terms used for the systematic literature review in Pubmed and Embase.

For the aim to discuss determinants and underlying mechanisms of CKD and RRT in immigrants, the included studies from the systematic literature search and reference lists were reviewed to find according literature. Additionally, supplementary articles was inquired looking for studies on genetics linked to CKD, as well as studies on the epidemiology of diabetes, hypertension and obesity in immigrant groups. Further, the association between LBW, PE and CKD in immigrants was studied and the frequency of LBW in countries of origin of immigrants and in offspring of the immigrants in the host county addressed. Later, social determinants of health such as "SES", "education", "culture" (though proxies like the use of traditional medicine, perception of disease and management, as well as beliefs or "attitudes"), and access to health care services were analysed using the databases mentioned. No ethical approval was necessary for this thesis. In this thesis, immigrants are referred to as ethnic groups, when described so in the studies. Furthermore, Western Europe is in the focus, and is - to simplify - referred to as "Europe" further in the text.

2.4.2 Study selection

For the systematic literature review, following inclusion criteria were applied: Studies since 1990 were included, because this was the year where CKD has been acknowledged as a separate entity in the GBD studies (26). Only studies written in English were considered. Studies that comprised specific information about the epidemiology (cause, prevalence, progression of CKD, incidence of ESRD, mortality under CKD) in adult immigrants in Western Europe were included. In the case of RRT, studies about the outcome on dialysis, as well as graft function, rejection and mortality after transplantation were included. Studies were included that contrast the health state of immigrants

either to the general population of the host country, or to the non-migrated population in the country of origin.

Exclusion criteria: Interventional studies, studies without a comparison group and studies including hospitalized patients or Roma were excluded. Roma, one of the largest ethnic groups in Europe, are a very specific group with distinct health issues and social challenges. The topic of renal health in Roma deserves an own, separate analysis that goes beyond the scope of this thesis.

3 Results

3.1 Systematic research on CKD in immigrant populations in Europe

A total of 245 citations were found, with 130 citation in the PubMed, and 115 citations in the Embase database. Sixteen citations were retrieved through reviewing reference of the included articles. After screening and sorting out according to the criteria described in Methods, a total of thirty-three articles on the epidemiology of CKD and RRT in immigrants in Europe were included (Figure 4).

Nineteen studies concerned CKD in immigrants in Europe (40-58). Fourteen studies were on RRT in immigrants in Europe (59-72). All studies from The Netherlands (NL), France, Sweden, Spain and Denmark referred to the country of origin to group the immigrant study population (53-58, 60, 64, 66, 67, 72). Only studies from UK referred to (self-reported) "ethnic groups" (40-52, 59, 61-63, 65, 68-71), There were twenty-one cohort studies (40, 43, 44, 47, 48, 50-52, 54, 55, 60, 62-68, 70-72), ten cross sectional studies (41, 42, 45, 46, 49, 56-59, 69), and two case-control studies (53, 61).
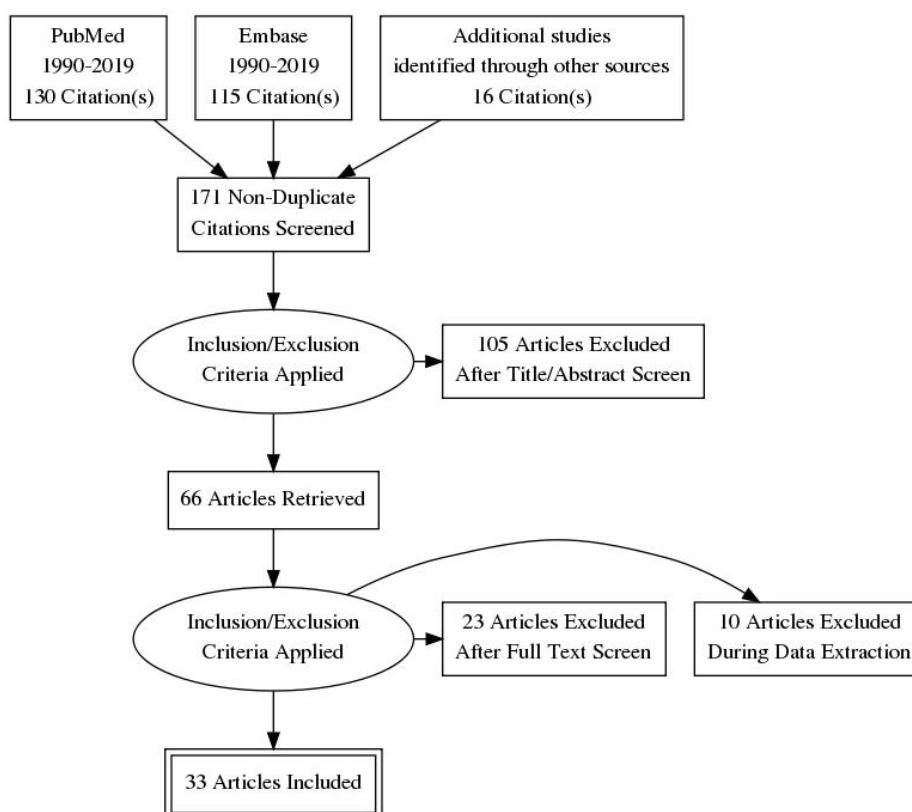
Figure 4: Flow diagram of studies included in the literature review. Generated with http://prisma.thetacollaborative.ca (39)

Replacing the search term "Europe" with "United States", revealed a more than three fold increased amount of titles (Figure 5).
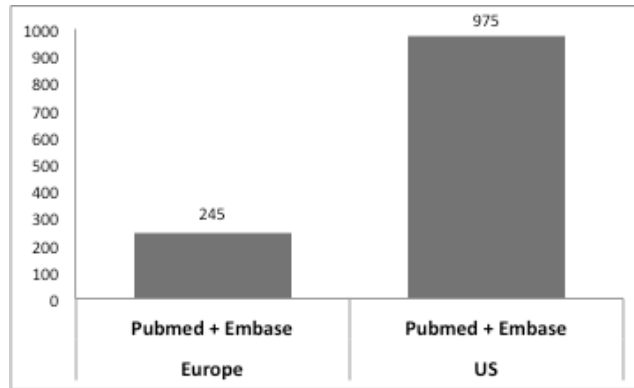
Figure 5: Comparing the number of articles on renal health in Europe and the US. Replacing the search term "Europe" with "United States" (US) reveals 975 studies, compared to 245 studies in Europe.

3.2 Epidemiology of CKD and RRT in immigrants in Europe

Findings on the epidemiology of CKD and RRT in immigrants in Europe are summarized in <u>Tables A1 and A2 in the Annex</u>. In the studies from UK, the populations "South Asians", "Indo-Asians", or "Asians" are mentioned. These terms are synonyms; they describe individuals from the Indian subcontinent, such as India, Sri Lanka, Pakistan, Bangladesh.

3.2.1 Causes of CKD and ESRD

The causes of CKD and ESRD in the studies included are summarized in <u>Table A3 in the Annex.</u>

3.2.2 CKD prevalence

South Asians (SA) and Blacks with diabetes in UK had a lower prevalence of CKD stage 3, though a higher prevalence of CKD stage 4-5 compared to the majority (45). Similar results were seen in a study with nearly 50'000 patients with hypertension in UK (46). In a study from 2013 assessing CKD in patients eligible for a UK cardiovascular screening programme, the prevalence of CKD was lower in SA as compared to the majority. This may reflect the younger age of SA, and the exclusion of diabetics, probably undermining the CKD prevalence in this population (49).

An increased prevalence of CKD was detected in all immigrant groups in NL, as compared to the majority (56).

Two studies compared the prevalence of CKD in non-migrated Africans to migrated peers: The multi-centre RODAM study (Research on obesity and diabetes among African Immigrants) assesses health of Ghanaian living in Ghana, Amsterdam, Berlin and London. There was a higher CKD prevalence in non-migrated as compared to migrated Ghanaian, particularly in non-migrated Ghanaian with diabetes and hypertension. In Ghana, the prevalence of CKD was lower in rural as compared to urban regions. In Europe, Ghanaian living in Amsterdam had a lower CKD prevalence compared to those living in London (57). The other study did not show a difference on the prevalence of diabetic nephropathy in migrated Cameroonians as compared to the

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majority with diabetes in France. However, similar to the RODAM study, there was a higher CKD prevalence in non-migrated as compared to migrated Cameroonians with diabetes (58).

3.2.3 CKD progression

Most cohort studies on CKD progression were performed in ethnic groups in UK:

In 1998, in a study with 39 patients with diabetic nephropathy, no sign for faster progression of CKD in SA living in Leicester was found (43). In another study with 329 patients with diabetic nephropathy, no difference in CKD progression within SA and Blacks as compared to the majority was detected (48). A study from 2015, where more than 1000 patients with CKD stage 3 where followed over 5 years, SA had similar CKD progression as compared to the general population (50).

In a small study with 45 patients followed over up to 4 years, an increased risk for progression of CKD due to diabetic nephropathy in SA as compared to Whites was found (44). Later, in a study with nearly 4000 patients with diabetes there was a faster progression of CKD in SA as compared to the majority over 5 years. Stratified by proteinuria, patients with proteinuria had a faster progression of CKD when they belonged to the SA or the Black ethnicity (47). The largest study with more than 6000 patients with diabetes and CKD, and a long follow-up of 9 years, an increased progression of CKD in Blacks and in Bangladeshi, though not in other SA ethnicities was observed (51).

One study assessed CKD progression in Black patient with CKD stage 4 to 5 in NL: Here, a higher eGFR decline was noted as compared to the majority. Accordingly, the RRT incidence was higher in this cohort followed over 13 months. Blacks were also referred later to renal services (55).

3.2.4 End-stage renal disease incidence

Most studies on ESRD incidence were performed in ethnic groups in UK. In the oldest study from 1992, the incidence of ESRD due to diabetes was 4-fold - and ESRD due to other causes even 14-fold higher in SA compared to the majority (40). Another study showed a 3-5-fold higher incidence of ESRD due to all causes, and a 5-fold higher incidence of ESRD due to unknown causes in SA (41), and similarly, Higgins et al., showed a 10-fold increased ESRD incidence in SA and in Afro-Caribbean in UK (42). A higher ESRD incidence was also seen in Blacks as compared to Whites in the cohort study of Mathur et al. (51). In 2019, a large cohort study with 17'000 patients with CKD 3-4, the incidence of ESRD was 60% higher in SA as compared the majority (52). The only study without a disparity was the one of Ali et al., where SA and Blacks had a similar ESRD incidence as compared to the general population in London (48).

Two studies addressed ESRD incidence in immigrant groups outside UK: In immigrants with diabetes in NL, Surinamese had a 40 times increased ESRD incidence as compared to Whites (53). In another study, a higher ESRD incidence was detected in many immigrant groups in Sweden, particularly in immigrants from Bosnia, Bulgaria, Africa, Turkey, Lebanon, Iraq and "other Asian countries". Interestingly, the offspring of immigrant groups also had a higher ESRD risk in the case of people with Bosnian, Lebanese background and from "other Asian countries" (54).

3.2.5 Mortality while CKD

Three studies on mortality of patients with CKD in ethnic groups in UK were found: In the cohort of Ali et al., there was no difference in mortality in SA, Blacks or White UK residents with CKD caused by diabetes over 6 years (48). Despite the faster progression of CKD in Bangladeshi, this ethnic group had the lowest mortality as compared to the general population. SA else also had a lower mortality on CKD as compared to Whites, though not as pronounced as Bangladeshi (51). In a study with more than 17000 patients with CKD stage 3-4, the SA population had a 25% lower mortality as compared to the majority (52).

3.2.6 Renal replacement therapy initiation rate

All studies assessing RRT initiation rate were from UK: Roderick et al., found a nearly 4-fold higher RRT initiation in SA and Blacks as compared to Whites in a study with 6000 patients (59). Later, a study based on the population of Birmingham found a 2-fold increased RRT initiation rate in SA and Blacks as compared to the Whites. The highest RRT initiation rate was seen in elderly patients (>70 years) of SA and Black ethnicity (65). A study from 2012 found distinctly increased RRT initiation rates in regions with high percentage of Blacks or SA, as compared to regions with many Whites (69):

3.2.7 Allograft survival and mortality after transplantation

Studies on graft survival and mortality after transplantation originated from UK, NL, France and Spain. The study from UK showed a higher risk for allograft loss and increased mortality after transplantation in SA as compared to the majority (62). The Dutch study, following patients over 6 month, did not find a difference of allograft survival between the majority and non-European immigrants. However, within immigrants, Arabian and African had a worse allograft survival as compared to the Asian study population (60). The French study did not find any differences in allograft survival or mortality in Africans in France and the majority, even though Africans had more often a delayed graft function after implantation (64). The Spanish study had the longest follow-up with up to 6 years: Here, African had more often rejection and loss of allograft function as compared to the Spanish. However, mortality was similar in the groups (67).

3.2.8 Mortality on dialysis

In the study of Prasad et al., there was no difference in mortality in SA, Blacks and Whites on dialysis in UK over 5 years (63). A large study with nearly 19´000 patients on dialysis in UK showed a clear lower mortality of SA and Blacks as compared to Whites over a follow-up of around 2.5 years (70). More than 1300 Blacks on dialysis where also followed-up over 5 years in a separate study, here they had a nearly 50% lower risk to die as compared to the majority (71).

Van den Beukel et al., studied mortality on dialysis in a composite group of non-European immigrants living in NL and Denmark: In NL, Dutch on dialysis had a nearly 2-fold increased mortality as compared to the immigrant group, where most had an African ancestry, followed by North African, Suriname, East Asian and Turkish origin (66). The study in Belgium comprised

again all immigrants, "Western", North African, SSA, West, East and SA in Denmark: The highest mortality was noted in Danes, and was around 2-fold increased compared to the non-"Western" immigrants. "Western" immigrants also had a survival benefit, though that was smaller and became less after 10 or 20 years of living in Denmark. The survival benefit in non-"Western" immigrants remained over time (72).

3.3 Determinants and mechanisms in CKD and RRT in immigrants in Europe

Determinants and underlying mechanisms involved in the disparity of renal disease in immigrants are summarized in Table A4 in the Annex.

3.3.1 Genetics

Some genetic traits, like APO1 mutations, have been associated with higher susceptibility to renal diseases, particularly in relation to hypertensive nephropathy and focal segmental glomerulosclerosis (FSGS) in African Americans (73). Friedman et al. have showed, that around 15% of African Americans have two such "renal risk variants" APO1 mutations, with a 10-fold increased risk for (non-diabetic) ESRD. European Americans have rarely such gene variants (74, 75). APO1 has also been linked to faster CKD progression in African Americans, irrespective of BP control (76).

MYH9, a gene closely located to APO1, has been linked to increased CKD prevalence in non-diabetic European Americans (77). Later, MYH9 has also been associated to diabetic nephropathy in the European American population with diabetes (75).

One of the very few studies on these genetic traits in Europe could not link diabetic nephropathy to either MYH9 or APOL1 in UK (78).

Tacrolimus, a main immunosuppressive agent after renal transplantation, has a different pharmacokinetic within individuals with African ancestry: Higher doses are needed to reach target concentrations. This may be a reason for more troubles with immunosuppressive treatment and a worse outcome in Blacks after transplantation, as too low levels are associated with rejection (79).

3.3.2 Epidemiology of diabetes mellitus and hypertension, obesity

Diabetes: Diabetes is distinctly more common in immigrants in Europe, in particular in SA, followed by North Africans, Middle Eastern and SSA. Within the SA population, there was a strong heterogeneity, with the highest prevalence of diabetes in Bangladeshi, followed by Pakistani and Indians (80).

Diabetes control (measured by HbA1c) was worse in immigrants, for example in SA and Middle Eastern/North Africans as compared to the majority in a Norwegian study (81). In a Swedish study, low SES was linked to worse glycaemic control in the primary care setting. Middle Eastern individuals had the worst HbA1c as compared to the general population in Sweden (82). Studies from Denmark indicated a more than 2-fold increased incidence and prevalence of diabetes in "Non-Western" immigrants, like SSA, Asians and Middle-Eastern people (83). Turkish and Lebanese had a particularly inadequate glycaemic control (84). All immigrants with diabetes, except SSA, had a lower mortality than the majority with diabetes (83)

Hypertension: In UK, hypertension was more common in SA and Blacks than in Whites. Hypertension control was less often achieved in Blacks, and more often in SA as compared to the majority (46). In a Dutch study, prevalence of hypertension was higher in all immigrants than in

the majority, except in female Moroccan. Hypertension control was also less often achieved in immigrants, despite high awareness for hypertension (85).

Obesity: A literature review on obesity in UK showed higher prevalence of obesity in Blacks as compared to the general population. Studies on obesity in SA living in UK were more ambivalent with results pointing towards higher or lower prevalence in this ethnicity compared to the majority (86). A study from Norway stratified weight according to origin: Turkish had highest prevalence of obesity, in particular women. The hip-waist-ratio was differently distributed, with highest ratios in individuals from Sri Lanka and Pakistan (Kumar et al., 2006).

3.3.3   Low birth weight and preeclampsia

A large population-based cohort study from Norway found a clear relation between LBW and a 70% increased risk for ESRD (4).

World wide, the prevalence of LBW has decreased between 2000 and 2005. However, still 14.6% of all new-borns are LBW. The highest prevalence of LBW is in SA and SSA (87).

Immigrant mothers have a 40% increased risk for LBW for their children world wide (88). For example in UK, all ethnic groups had more LBW in their offspring as compared to the majority, in particular Indian and Pakistani (89). A Swedish study also showed a higher risk for LBW, especially in SA and SSA immigrants (90).

There is a link between SES, education and LBW: Low SES and education are associated with an increased LBW risk, and discussed as a reason why mothers form SSA have an more LBW children in Belgium (91).

Generally, PE seems to be more rare in immigrants as compared to the general population in HIC (92-94). However, within the immigrant population, those from SSA and Caribbean/Latin America had the highest PE risk. Compared to the majority, SSA had a higher PE risk in Denmark (OR 1.2), Spain (OR 2.4) and Sweden (OR 1.2) (92). In Norwegian studies, all immigrant groups had lower PE risk, except those from Somalia and Philippines. Duration of stay was linked to an increased risk for PE in all immigrant population, with Somalian having a higher PE risk compared to the general population more than 5 years after immigration (93). The PE risk was related to cause of migration, with lowest risks in work immigrants, and highest risks in refugees. However, also refugees had generally less PE than the majority in Norway (94).

3.3.4   Socioeconomic status, social deprivation, education and profession

Low SES is clearly related to the increased occurrence of CKD and higher mortality (37, 95). A literature review on patients with CKD stage 3-5, found that low-income class, "not owning a house", low education and lack of health insurance were linked to higher mortality and risk for cardiovascular incidents as compared to counterparts (38). Furthermore, low neighbourhood affluence, low income and education was linked to increased progression of CKD - independently of diabetes or hypertension (96).

Individuals with lower SES presented to renal services with more advanced CKD as compared to individuals from higher SES, as shown in UK (97). Social deprivation was also linked to a higher RRT incidence and worse survival, regardless of ethnicity (98).

Comparing the US with NL, which has universal health care coverage, low income was a better predictor of a higher CKD prevalence in the US - whereas it was low education that had the strongest association to CKD in NL, showing the importance of free health care services on CKD (99).

In a study from Amsterdam, lower educational and professional degree was linked to a higher occurrence of CKD as compared to those with a higher attainment - irrespective of the origin (100). However, upon statistical controlling for CKD risk factors, most immigrant groups - except SA Surinamese and Dutch - lost this association. Educational and professional degree thus did not explain all of this disparity seen in immigrants as compared to the majority (56).

3.3.5   Culture shaped habits, perceptions and attitudes

Proxies like the use of traditional medicine, perception of disease and management, and beliefs or "attitudes" were used to assess how culture influences kidney diseases in immigrants.

Traditional herbal medicine can be nephrotoxic and lead to acute and chronic kidney injury. In an interview-based study with Surinamese in NL, 75% used traditional herbs - to promote their health, for prevention and to treat conditions. This was independent of salary or degree. Reasons for intake of such medicines where "habit since childhood" and belief that herbs work better and have less adverse effects than school medicine (101).

In a qualitative study in Surinamese and Ghanaian in NL, both groups tend to stop or reduce the dose of antihypertensive treatment and preferred traditional treatment strategies. They were concerned about "chemical compounds", becoming addicted, adverse reactions, sexual function and costs. Importantly, "trusting the physician" positively influenced intake of antihypertensives (102).

Culture also influences dietary habits: A qualitative study in Bangladeshi in UK highlighted the belief, that unsalted, "unspiced" food is less digestible and that only spiced food benefits health (103). Such attitude may influence salt intake and promotes hypertension and CKD progression.

Culture also shapes an individual´s perception of what is "healthy" or "beautiful". In a literature review on how African immigrants in Europe perceive body sizes, low SES and segregation was linked to the tendency to prefer high body weight. Higher SES and "urban lifestyle" was linked to preferring low body sizes. Additionally, the author observed that the more "European" someone was, the more dissatisfied African where with their sizes (104).

Organ donation is less common in SA in UK (105). In questionnaire-based in Spain, Nigerian immigrants had a distinctly worse attitude towards living kidney donation as compared to Spanish or other European immigrants (106). How immigrants stand in the context of transplantation, seemed to be dependent of the host country: Uruguayan immigrants living in

Spain were in favour of donating a kidney during life or after death, as compared to those living in the US, where only half considered kidney donation (107).

In a study on life quality in SA on RRT in UK, SA had a worse life quality as compared to whites, even though dialysis quality was similar. This was particularly true in PD. In HD, SA and Whites had a similar life quality, though Whites had more other health conditions (108).

3.3.6 Migration

The RODAM study compares health in non-migrated Ghanaian and in migrated Ghanaian living in Amsterdam, Berlin and London. This allows estimating health conditions before migration (corresponding to the "pre-migration" phase), and in the host country (including aspects of the "transit phase" and arrival at destination, the "host country").

Generally, smoking is rare in Ghanaian. However, upon migration to Europe, smoking prevalence increases substantially, independently of educational degree or profession, and is especially common in Amsterdam and Berlin (109). The prevalence of obesity was drastically increased in men in urban Ghana (4-5-fold), and even more upon migration to Europe (15-fold), as compared to those living in rural regions in Ghana. Diabetes was more common in the urban environment in Ghana and similarly higher in migrated Ghanaian, as compared to Ghanaian living in rural areas (110). Hypertension showed a similar pattern like obesity. However, the awareness of high BP was best in migrated Ghanaian, as compared to the non-migrated peers. Still, around half of all migrated Ghanaian with high BP were untreated (111).

Another RODAM study revealed that it is lower SES and educational degree, which is linked to more diabetes in urban Ghana and migrated Ghanaian in Europe. However in rural Ghana, it was the affluent and educated people that had a higher occurrence of diabetes (112).

Upon arrival in Canada, dietary habits in immigrants are healthier than in Canadians. However, dietary habits deteriorate along increasing duration of stay, with immigrants consuming increasingly caloric rich food. A reason for this dynamic was the low SES in these immigrants (113).

Increasing duration of stay in the host country was also linked to higher BP worldwide, particularly in people migrating from rural to more urbanized regions. The BP increase seem to be unrelated to the BMI (114).

3.3.7 Access to health care services

A literature review on health care utilisation pointed towards immigrants using services less often than the majority. The use was dependent of the origin, reason for migration and also language skills. However, results and population had a very heterogeneous behaviour (115).

A register-based study from Norway showed that immigrants from HIC above 50 years of age used primary health care less often than the majority. However, immigrants from LMIC also attended less often to primary health care, though not before 65 years of age. Refugees had more, working migrants less contact with primary care providers. Duration of residency was linked to increased use (116).

Delayed referral of patients with advanced CKD to specialised nephrology care was linked to worse outcome, higher mortality and less access to transplantation in an Australian study. Timely referral is thus important for the outcome of patients with kidney diseases (117).

A study from UK showed, that low SES, and not ethnicity, that was linked to late referral and to less chance to be listed on transplantation waiting list. The only ethnicity related difference was found in elderly patients: Here Whites had a lower chance to be listed for transplantation than Blacks or SA (118).

3.3.8   Other aspects

NSAID, often used as analgetic or anti-inflammatory drugs, can cause CKD by different mechanisms. In some countries, like in UK, they can be bought without prescription. In a study from UK, fewer NSAID were prescribed to SA and Blacks as compared to the majority with CKD. The lower the kidney function, to less NSAID was given. Thus, NSAID consumption is not seen as a reason for more ESRD in ethnic groups in UK (119).

4 Discussion

CKD is a very common NCD that has a high morbidity, mortality, and high costs, particularly in RRT. In future, the prevalence of CKD is expected to rise, especially due to an increased occurrence of diabetes and hypertension linked to obesity. There are 75 million immigrants in Europe, and most countries are multi-national. The health state of immigrants is crucial for the health related policy making in the European countries.

The aims of this thesis were to describe the epidemiology of CKD and RRT in immigrants in Europe, to discuss underlying determinants and mechanisms of the renal health disparity, and to find gaps of the existing research on this topic.

As described in chapter 2.1.3, migration is an independent determinant of health and influences the health state of immigrants in a complex, dynamic way, and intersects with all determinants of health. The theoretical framework presented in Figure 3 is helpful to analyse different aspects and factors affecting life circumstances and health at different time points in an immigrant´s life, as it depicts the main phases of migration, the pre-migration phase in the home country, the transit phase, and the arrival at the host country.

Migrant´s health studies tend to compare immigrants to the general population. However, to study the effect of migration, immigrants should also be compared to the non-migrated peers in the country of origin. Even though the migrating population might defer significantly from those not migrating, only such a comparison can contrast health in the pre-migration, to the destination/host country phase. Such analyses have been performed with the RODAM studies.

Acculturation can be defined as the process in which people from a particular culture are being exposed and are adapting to other living circumstances, including e.g. the climate, eating habits, work life, social networks and also to other culture. The interaction with living circumstances and culture of the host country and the degree of acculturation influences health. Acculturation is often measured by variables like "duration of stay" or "language skills" (120, 121).

4.1 CKD in immigrants in Europe

The systematic literature review yielded 33 articles. Most studies originated from UK, reflecting that UK has the highest rates of ethnic groups on dialysis in Europe, and that self-reported ethnicity is collected in UK Renal Registry (UKRR) since the 80s (98, 122). Many of the studies included outcomes on advanced CKD or ESRD. This may be linked to renal registries mainly collecting data when patients reach CKD stage 5 or when starting RRT, probably because this is a defined population managed by renal services.

The studies included indicate a higher prevalence of high stage CKD (stage 4-5) in immigrants in the European countries studied. For example in UK, CKD stage 3 was similar in SA or Blacks as compared to the majority, though higher stages were more prevalent in these groups (45, 46). The Dutch study further supports the increased prevalence of CKD in immigrants (56).

At first sigh, result of studies on CKD progression in ethnicities in UK seem ambiguous, with three studies failing to find any disparity as compared to the majority (43, 48, 50). However, larger studies clearly indicated a faster progression, especially in diabetics, and in Blacks and Bangladeshi in UK (47, 51). Additionally, the increased ESRD incidence and RRT initiation rate in SA and Blacks in UK as compared to the majority further support these findings (52, 65, 69). In Europe, immigrants in NL and Sweden also had a higher ESRD incidence possibly indicating faster CKD progression as compared to the majority (53-55).

There is not much evidence on the outcome of immigrants in Europe after transplantation. Results were conflicting as some studies showed an increased risk for kidney graft dysfunction (62, 67) and mortality (67), and some no difference. Immigrant groups were heterogeneous here, with different risks for graft function within the populations (60). The French study indicated more "delayed graft function" in Africans than in the majority. However, a reason was that individuals with African origin more often lived in the (French) Caribbean, and traveling to France to transplantation, delayed implantation after the organ is harvested, which is a risk factor for impaired function. However, Africans did not have more troubles survival of graft as compared to the majority (64).

In conclusion, studies from UK, Netherlands, Denmark, Sweden, Spain and France indicate a higher prevalence and a faster progression of CKD, as compared to the majority. The outcome after transplantation may be worse in immigrants, though there are only a few studies and results are conflicting.

4.2   Determinants and mechanisms

4.2.1   Causes of CKD in immigrants in Europe

The causes of CKD in immigrants in Europe were different as compared to the majority, and reflect the epidemiology of CKD in the country of origin, and in the host country in Europe. Infectious diseases like chronic pyelonephritis or Tb-related CKD were more common in SA or Blacks compared to the majority in UK (41, 59, 64, 67). This reflects that in LMIC regions, such as in SSA, the causes for CKD more commonly than in Europe include infections like HIV, viral hepatitis, schistosomiasis or malaria (123). Clearly, an important difference is that individuals with African or also Asian genetic background do not have polycystic kidney diseases, which is responsible for around 5-8% of ESRD in the general population in Europe and in the US.

Results also indicated a higher occurrence of glomerulonephritis in the immigrant populations studied (Table A3). It is unknown, if this is related to a genetic predisposition, or is a consequence of more infections, that can elicit such autoimmune reactions. A difficulty is, that

late stage kidney disease is reflected by kidney fibrosis in the histology - irrespective of its original cause. In such cases, glomerulonephritis cannot be diagnosed anymore, and the cause of CKD is clinically interpreted as diabetic or hypertensive nephropathy, or "other causes", even though it is in reality a glomerulonephritis. The number of glomerulonephritis may therefore be generally underestimated, especially upon late referral to renal services.

In the studies included, CKD due to hypertension seemed to be particularly common in individuals with African ancestry, and CKD due to diabetes in Asian populations, as compared to the majority (Table A3). This may reflect the increased prevalence of diabetes and hypertension in immigrants in Europe, and possibly an increased genetic susceptibility for hypertensive nephropathy in individuals with African ancestry.

APOL1 has been linked to increased risk for CKD in individuals with African ancestry and has gained a lot of attention the past years. APOL1 codes for the protein apolipoprotein L1, involved in renal vascular and epithelial integrity. Thus, "risk variants" of APOL1 may lead to tissue dysfunction and increased susceptibility to CKD (74). These APOL1 risk variants were shown to promote resistance to the African sleeping sickness, a parasite infection transmitted by tsetse flies. It was thus hypothesized, that APOL1 variants involve a survival benefit and thus were positively selected during evolution, and therefore more common in individuals with African Ancestry (73).

APOL1 has particularly been studied in African Americans, where it was strongly linked to increased hypertension related ESRD and FSGS (74). However, from reviewing the literature, no study analyses the association of APOL1 risk variants with CKD in individuals with African ancestry in Europe. It can be hypothesized, that risk variants are also preserved in this population and are a cause for increased prevalence and progression of CKD in immigrants with African origin in Europe.

The discrepancy in metabolism and pharmacokinetics of <u>Tacrolimus</u> in people with African origin may complicate management after transplantation and lead to more complications like rejection reactions. However, as mentioned, it is unknown if individuals with African ancestry in Europe have a worse outcome after transplantation as compared to the majority.

4.2.2 Diabetes, hypertension and obesity in immigrants

A main reason for the higher CKD prevalence and progression in immigrants in Europe is the <u>high prevalence of diabetes, hypertension and obesity</u> in in many immigrant groups, as compared to the majority. Additionally, several studies indicate that diabetes and hypertension control is less often achieved in immigrants, even though awareness exists (81, 82, 84, 85). There is a large heterogeneity within immigrants, for example even though Bangladeshi had a clear excess of diabetes, they had less overweight as compared to other SA and to the host population in Europe (80).

Generally, the occurrence of diabetes and obesity is increasing globally, particularly in LMIC, the origin of many immigrants in Europe (28). The RODAM studies found a higher prevalence of diabetes and obesity in urban as compared to rural Ghana, and an even more increased occurrence upon migration to Europe (110, 111). Smoking was also more common after Ghanaian migrated (109). Migration seems thus to be linked to more diabetes, obesity and smoking.

Studies have found, that acculturation, as measured by duration of stay, is related to worsen health, e.g. to deteriorating dietary habits, increasing body size, and increased BP (113, 114). A reason may be, that immigrants change their lifestyle, particularly after adapting to the new culture, with more sedentary occupation, and possibly less physical activity as before migration. There is also the phenomenon of "nutritional transition", describing a transition from a healthier diet towards a "Western" nutrition, which is more caloric and includes more animal fat (124). The "thrifty phenotype" hypothesis suggests, that stressors like food insecurity and hunger during foetal development and early life lead to metabolic (and behavioural?) changes, that are linked to weight gain, obesity and diabetes later in life (125). Additionally, it is hypothesized, that the exposure to a new culture is "stressful", affecting particularly BP (114).
It is possible that such mechanisms also affect the increase in diabetes, hypertension, obesity, and finally CKD in immigrants in Europe.

4.2.3 Low birth weight

LBW may also play a role in the excess of CKD in immigrants in Europe. Since the 90s, low birth weight (LBW) has been linked to renal diseases later in life {Mackenzie, 1996 #6308}. Later, a large population-based Norwegian study observed a 70% increased ESRD risk in those with LBW. LBW is associated to preterm birth and impaired growth during pregnancy. The mechanism may reflect intrauterine kidney development where most nephrons develop in the last trimester. In the case of impaired growth and development, less nephron numbers are achieved, and a "reduced nephron reserve" is present at birth, with a higher risk of deterioration of the renal function later in life (4). In the US, LBW has been identified as a reason for the ESRD surplus in African Americans compared to European Americans (126).

In Europe, to our knowledge, there are no studies directly linking LBW to the excess of CKD in immigrants. However, LBW is related to low SES and it is estimated, that 95% of all LBW children are born in LMIC, most in SSA and SA, where many immigrants in Europe originate from (87, 127). Thus, LBW in the country of origin may affect the risk of getting CKD and ESRD after migration.

Table 2 reflects the high prevalence of LBW and preterm birth in SSA, SA, South East Asia and Sweden, as published by Blencowe et al. in The Lancet (87, 127). To compare, the risk for ESRD in Sweden is increased in immigrants from these regions, as compared to the majority (54). This

may indicate a causal link and it can be hypothesized, that the higher LBW prevalence in these immigrant groups is a reason for the increased risk for ESRD later in life.

Prevalence LBW (87)	Prevalence preterm birth (127)	Risk ESRD in Sweden (54)
Sweden: 2.4%	Sweden: 6.1%	Majority in Sweden: HR 1
SSA: 14.0% (12.2-17.2%)	SSA: 12.3%	Immigrants from SSA HR men 2.1 (1.7-2.6) HR women 1.8 (1.2-2.6)
SA: 26.4.3% (18.6-35.2%) SEA: 12.2% (9.5-14.6%)	SA: 13.3% SEA: 13.6%	Immigrants from SA and SEA HR men 1.8 (1.5-2.2) HR women 1.4 (1.1-1.8)

Table 2: Comparison of the prevalence of low birth weight (LBW) and preterm birth in SSA (Sub-Saharan Africa), South Asia (SA) or South East Asia (SEA) and Sweden (left and middle panel), as compared to the risk of ESRD in immigrants from SSA, SA or SEA and the majority in Sweden.

Additionally, several studies showed an increase risk for LBW in the offspring of immigrants as compared to the majority in UK, Sweden, Belgium, and also in literature reviews worldwide (88-90). LBW was also linked to low SES and education (91). This may lead to a higher CKD risk in the offspring of immigrants in Europe, and represent a mechanism linking social disadvantage with CKD especially in disadvantaged immigrant groups. In fact, Wandell et al. showed that some offspring of immigrant in Sweden do have a higher ESRD risk as compared to the majority: Particularly those with a background from Bosnia, Turkey, Lebanon, and from "other Asian countries" had more ESRD compared to the majority (54). The CKD or ESRD risk in offspring of immigrant in other European countries is not known.

4.2.4   Preeclampsia

PE is clearly linked to CKD and ESRD in mothers later in life, though the relation to the excess of CKD in immigrants in Europe seems unclear. Generally, PE is less common in immigrants as compared to the majority in HIC. However, immigrants originating from SSA had the highest PE risk within the immigrant groups, and also a significant increased PE risk as compared to the general population in Denmark, Spain or Sweden (92). Accordingly, in a Norwegian study, Somalian had the highest PE risk (93). Importantly, the cause of migration, and acculturation affected PE occurrence: Refugees had the highest PE risk (although still lower than the majority), and immigrants generally had an increasing PE risk along increasing duration of stay, with Somalian women reaching a 60% higher PE risk then the majority (93, 94). PE may therefore be linked to the higher risk of CKD in some immigrant subpopulations, like individuals from SSA.

4.2.5 Relation of socioeconomic status and renal disease

There is also a clear link between <u>lower SES, low degree education, profession and CKD</u>. This may be an important cause for the increased prevalence of diabetes, hypertension, obesity and CKD, and CKD progression in immigrants in Europe. The relation between these variables and CKD is complex. A model reflecting pathways and mechanisms is presented in <u>Figure 6</u>. Social deprivation includes a lower SES, income, low degree education and profession, and also "living in less affluent areas". Ethnicity and migration is linked to social deprivation. Social deprivation is interlinked with barriers to access to health care services, unhealthy behavioural and dietary habits, and issues of compliance to treatment and follow-up. All of these factors are associated with more infections, possibly intake of nephrotoxins, CKD related diseases, and LBW. Stress, discrimination, mental health issues and substance abuse may negatively influence all of these pathways. Ageing further naturally increases the risk of chronic diseases and CKD. There is a bidirectional link between social deprivation and CKD; social deprivation is associated with CKD, and CKD leads to social deprivation, a vicious circle (37, 128). To our knowledge, the UKRR, is the only renal registry in Europe collecting data on social deprivation (98).
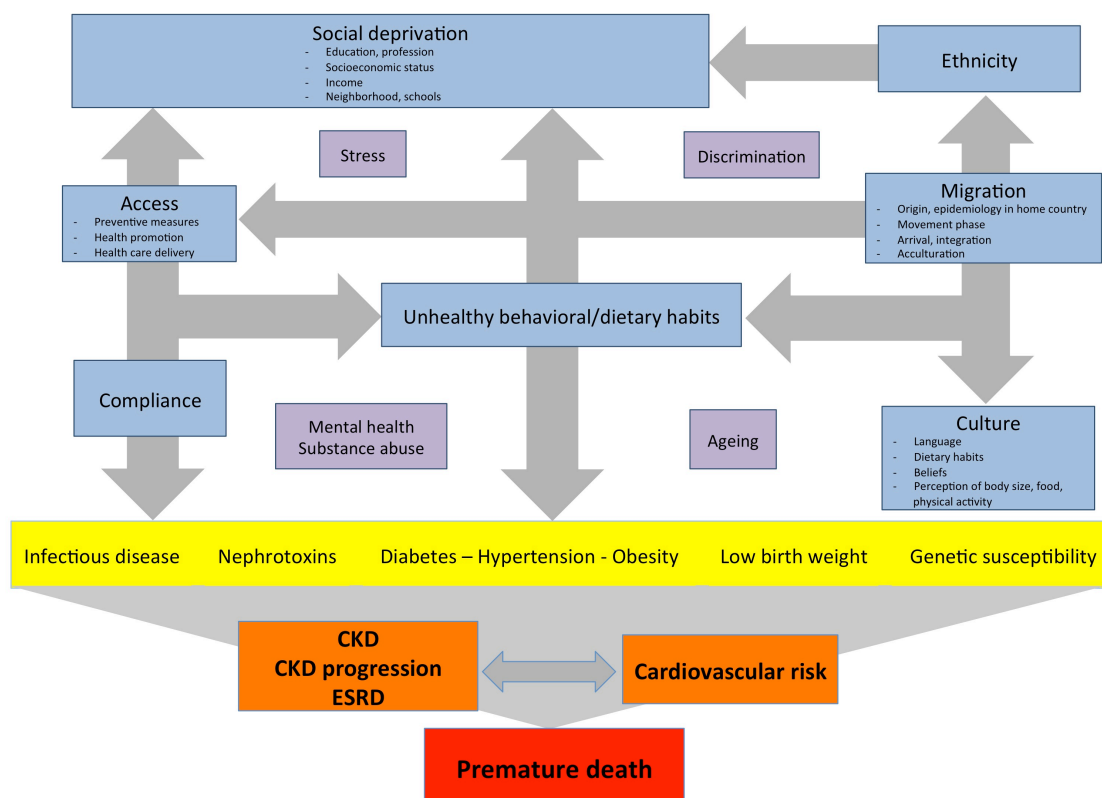

Figure 6: Interplay of social deprivation, ethnicity, migration and CKD. There is a bidirectional relation of social deprivation and diseases leading to CKD and premature death. Adapted from Nicholas et al., 2015, with permission (37).

The increased prevalence of diabetes, hypertension, obesity and CKD in immigrants may also reflect the "Diffusion theory". This describes effects linked to the "epidemiological transition", which consists of a natural decrease of communicable, and an increase of NCD in populations developing from low to higher income. Affluent people were the first to experience an increase in NCS, because they could afford e.g. smoking, high caloric nutrition, and had more sedentary work. However, later in time, this trend and differences have been seen to "diffuse": It is thought that the less affluent population groups "caught up" with an unhealthy lifestyle and experienced an increase in chronic diseases - while the affluent group adopted a more healthy behaviour and lifestyle (129).

Education and profession may be linked to renal disease - independently of origin or ethnicity. In NL, immigrants attain a lower degree education and profession as compared to the majority, and this was postulated as a reason for more CKD in these groups (56). However, in secondary analyses, there was a differential effect of education and profession for the immigrants and the majority: The general population consistently had a relation of lower degree education and profession, and higher CKD risk. However, in immigrants, controlling for gender and age annihilated the effect of education and profession to CKD in all groups, except in SA Surinamese (100). Low degree education and profession thus explained a part of the difference of CKD prevalence in immigrants and the majority, though not all. Suriname has been a colony of NL, and thus, Surinamese speak Dutch and are - from a culture perspective - closer to Dutch than other immigrants. This may be a reason for the similar results and positive effect of education and profession on CKD in these groups. In contrary, e.g. in Turkish or Moroccans, high educational degree is less "protective", which may imply other risk factors, like behavioural, dietary habits, issues with language skills or access to public preventive measures as factors causing more CKD (100).

4.2.6   Aspects related to culture

Culture influences what kind of traditions, habits, beliefs, perceptions or attitude an individual has. Differences in such habits may be unfamiliar to the health provider and make a difference in the presentation, development or management of CKD. Such culture shaped factors may play an important role in the context of CKD, e.g. when it comes to the use of potentially nephrotoxic traditional herbal medicines, compliance to treatment, unfavourable diet habit, body size ideas and opinion on kidney donation.

There is a known association between the widespread use of traditional herbal medicine and acute kidney injury leading to CKD (30, 123). Herbal medicine is very common in some immigrant groups, and may be co-responsible for the increased prevalence and progression of CKD in immigrants in Europe. Problems are a possible nephrotoxic effect, interactions with other drugs, and prioritisation of traditional medicine over e.g. antihypertensive treatment prescribed by the school medicine physician. The qualitative study in NL observed that African Surinamese

and Ghanaian stopped BP medication due to distrusting "chemical compounds" and side effects concerns, like addiction or interference with sexual activities. Culture related beliefs of what "pills", or "Western medicine" represents, may also play a role. Importantly, good communication and physician-patient relationship positively affected BP treatment adherence (102).

Perception of what looks "beautiful" or "healthy", is shaped by culture (104). In earlier studies in SSA, it was seen that many young women preferred overweight - a normal BMI was considered "thin" and related to wasting diseases like HIV or Tb. Overweight was associated with being social, and symbolized a higher status, wealth and health. Accordingly, only resourceful people could afford the food and lifestyle promoting higher weight (130, 131). In HIC (and increasingly also in countries in transition), high SES is linked to lower body weight, and it is the less affluent that tend to be obese (132). Such differential body size ideals have also been observed within SSA immigrants in Europe: Those living in lower socioeconomic circumstances, or segregated from the majority, favoured higher body sized. SSA living in urban Europe or in higher socioeconomic circumstances, preferred a slim appearance (104).

Culture also influences dietary habits, which are important in the context of CKD, as high sodium, potassium and phosphate intake can worsen volaemia, hypertension, hyperkalaemia and mineral and bone disorder - promoting CKD progression and increasing mortality. Patient with advanced CKD are advised to reduce intake of these electrolytes, which include for example less salting of the meals, and refraining from potassium rich (e.g. beans, spinach, potatoes, fruits like banana and oranges) and phosphate rich (e.g. chicken, pork, chocolate and cheese) food. The qualitative study addressing diet in Bangladeshi in UK points towards a "conflict of interest" between eating and cooking preferences and recommendations (103). Eating and cooking habits may thus also interfere with CKD management and promote CKD progression and complications in some immigrants in Europe.

Some studies suggest less living and deceased kidney donations within immigrants (105, 106). Less living kidney donation, particularly to relatives may be a reason why immigrants have a longer time on the waiting list and potentially a worse outcome as compared to the majority. Living kidney donation is the best possible match, particularly when related, and has the best outcome in the context of RRT.

Acknowledging, respecting and addressing such differential ideas in the use of traditional medicine, body size ideals and dietary habits, is part of the cultural competence of health care providers, allowing intercultural communication and a good physician-patient relationship.

4.2.7   Access to health care services

Access to health care services and health care utilisation in the host country may also play a role in the disparity of CKD and RRT in immigrants in Europe.

Timely referral to specialised renal care is important for management and outcome of patient with CKD, and delayed referral is linked to higher mortality and less access to transplantation (117). There are no studies specifically discussing utilisation of renal services in immigrants.

Generally, immigrants utilize health care services less often than the majority. However, there are large heterogeneities, depending on age, origin, socioeconomic circumstances in the origin, reason for migration, and e.g. language skills (115).

UK, Netherlands, Denmark, Sweden, and Spain, where most studies are from, are countries where patients need to be referred to specialists by primary care providers, like general practitioners. If there is a barrier to primary care services, there may also be a barrier to renal care. Access to primary care services is thus central.

The study of Diaz et al. demonstrated that utilisation of primary care in immigrants in Norway is dependent on age, origin and cause if migration. Elderly immigrants from LMIC had distinctly less contacts to primary care than the majority. Such an individual, with progressing CKD, may thus have less chance to be referred to specialists. Duration of stay was linked to the increased use of services (116). This may reflect worsening of the health state of immigrants along duration of stay, as described below.

A few studies included in the systematic review, indicate that immigrants are referred later as compared to the host population. For example in van den Beukel et al., (55) individuals with African ancestry had a lower renal function when they were referred to specialised "pre-dialysis" care.

In the context of renal transplantation, studies point towards less access to transplantation waiting list in social disadvantaged individuals: Udayaraj et al. showed, that (upon controlling), it is not ethnicity, but SES, that is linked to a lower chance for listing to transplantation in UK (118). Along these results, the worse outcome in immigrants after transplantation in some studies included may reflect the SES, and not ethnicity or the immigrant status.

The high prevalence of CKD in SSA, like in Ghana, has been associated with poor access to primary care, and is described as a reason why Ghanaian have more CKD in Ghana, as compared to those who migrated to Europe. It is also postulated that the lower CKD prevalence in rural areas owes undiagnosed CKD cases and is thus underestimated (57).

It is unknown, how barriers to access to primary care during transit, potentially leading to discontinuity of treatment for e.g. high BP or diabetes, influences CKD later in life.

4.2.8 Other aspects

The use of NSAIDs can contribute to CKD or worsening of established renal diseases. In many countries in Europe, NSAIDs can be bought over the counter, and this consumption is not regulated. One study on immigrants with African origin in NL did not find an increased prescription of NSAIDS in immigrants as compared to the majority with CKD and thus could not link NSAID as a cofactor affecting CKD occurrence in this group. How the over-the-counter-use of NSAIDs is not monitored and the effect on occurrence and progression in immigrant is unknown.

4.3   Survival on dialysis and the "healthy migrant effect"

Immigrants are generally healthier than the majority, and exhibit different health benefits, like generally lower mortality or less cancer. This observation is often described as "healthy migrant effect". In the context of renal diseases, such an effect is seen in the superior survival of immigrants on dialysis as compared to the majority in UK (Blacks and SA), NL and Denmark (66, 68, 70-72). Additionally, CKD was less common in the migrated Ghanaian, as compared to the non-migrated peers in Ghana in the RODAM study (57).

Different mechanisms leading to this apparent health advantage have been discussed.

To begin with, there may be a "selection bias"; Immigrants are supposed to be healthier than the population in the country of origin, as it needs certain "fitness" and resources to be able to migrate at all (35). In the case of renal diseases, it has also been suggested, that the general population in host countries have better access to transplantation, and thus only leaving elderly, sick patients on dialysis. However, in Europe, there are no signs for less access of immigrants to transplantation (118, 133).

Additionally, some immigrant groups have lower cardiovascular risk, and less ischemic heart diseases than the majority (18, 134). In SSA this has been associated to less dyslipidaemia and less smoking (134). However, stroke is seen to be more common in SSA, the role of CKD for that is unknown (134).

Elderly immigrants tend to migrate back to spend their last days of life in their home country. Return migration may thus reduce the disease burden in immigrant populations in the host country, also called the "Salmon bias" (33).

Furthermore, a "Survival bias" may elicit the impression of healthier immigrants on dialysis. This bias suggests, that only the healthier immigrants survive, reach ESRD and the need for RRT, and that many others die early and are not "caught up" in in the cohort studies. However, Ali et al. did not detect an increased mortality in SA or Blacks with CKD as compared to Whites in UK (48).

Despite an - at least initial - health advantage, immigrant's health deteriorates over time and mortality increases along duration of stay; Immigrants tend to adopt unhealthy diets, and are affected by weight gain, more diabetes, high BP, more PE, preterm birth, and also cancers, like breast cancer (34, 35, 93, 113, 114). More research is needed to assess mortality over time in patients with renal diseases, and looking at immigrant's health clearly necessitates the inclusion of the duration since migration-factor to account for dynamics related to acculturation.

4.4 Gaps of existing research on CKD in immigrants in Europe

Generally, there is scarce literature on the epidemiology of CKD and RRT in in Europe. This is compared to the US, where there has been a large interest in renal health of immigrants and also African Americans, in which most studies on renal health are conducted (Figure 5).

Most studies originate from UK and NL. To our knowledge, there are no studies on CKD or RRT in immigrants in other immigrant rich countries, particularly Germany, which has the highest numbers of immigrants in Europe, or also Switzerland. Clearly, data on these, and many other (Western) European countries are missing.

Scandinavia is known for its registries and facilitated alignment of different population registries that is enabled by a unique ID-number. Interestingly, there are studies from Sweden (although only one), and there is an interest on immigrants on dialysis in Denmark. The only Norwegian study available compares CKD in Norwegians to the American population (135). Up to now, there are no studies from Norway discussing CKD or RRT in immigrants yet.

When it comes to the immigrant populations addressed, only one study assessed CKD risk in immigrants from Eastern Europe, showing a distinctly increased ESRD risk in immigrants from Bulgaria and Bosnia (54). Eastern Europeans are a large immigrant community and there is a clear gap for research on renal health in this population.

As seen in different studies included in this thesis, there is a distinct heterogeneity within the immigrant population, and that is an issue in studies addressing broad groups, like "SA" or "Blacks". The term "SA" includes multiple countries and around 1.7 billion people who differ significantly from each other by living circumstances, lifestyle and culture, and who cannot be addressed as one study population. This is reflected e.g. in the differential prevalence of diabetes, hypertension and obesity in Bangladeshi (80, 136), or the differential prevalence of BP, awareness and BP control in African from different SSA countries (85). Generalisation of immigrant into large regional groups or ethnicities can undermine health disparities, and stratification into sub-groups can give rise to different CKD causes, occurrence, progression and mechanisms.

Ethnicity is mostly used in the studies from UK. Issues with grouping individuals by "ethnicity" as compared to "country of origin", is that ethnicity is dynamic and can change during life. Ethnicity does also not necessarily represent the region of origin, and does not include the country of origin (that can help to assess the health state during the pre-migration phase), the cause of migration (like working, family reunification, refugee; or voluntary/forced migration), and particularly acculturation, which is - as seen in this thesis - crucial to analyse the dynamics of immigrant´s health over time. Additionally, ethnic groups potentially not only include immigrants, but also their relatives or offspring born in the host country. These individuals

constitute a separate population and cannot be combined and studied with immigrants as a "whole".

Furthermore, to study the effect of migration on an individual´s health, immigrant population have also to be contrasted to the non-migrated peers, as this has been performed the RODAM study. Even though immigrants do not represent well the general population of the host country, comparing the migrated to the non-migrated can give rise to findings that are important for migrant's health and may reflect "migration" as an own mechanism, including the health state in the pre-migration phase, and aspects related to the transit phase. There is a clear gap in more such studies involving different populations and origins.

CKD causes: Although there are many other reasons for the increased burden of renal diseases in immigrants in Europe, genetics may also play a role. Interestingly, "renal risk variants" are extensively studied in African Americans, but not in immigrants with African Ancestry or "Asians" in Europe. Finding "renal risk variants" in different populations may allow detecting those at high risk for CKD progression and elicit a different monitoring and management.

LBW may significantly affect the occurrence of CKD in immigrants and also in their offspring in Europe. There is a clear gap linking and assessing the role of LBW for the excess of CKD in immigrants in Europe. PE, also linked to renal disease, seems to be less of a risk in many immigrant populations. However, again, studies have found that some subgroups have a higher risk (e.g. Somalian in Norway), and thus may be more prone to develop CKD later in life. Thus, there is a research gap on the role of both LBW and PE in CKD.

CKD in offspring of immigrants in Europe has only been addressed in a Swedish study, showing an increased ESRD risk in particular subpopulations. This requires addressing renal diseases in individuals with immigrant background.

Mortality seems to be lower in immigrants on dialysis. The reasons are only hypothesised and demand further research, also in other immigrant populations and host countries. Findings could help the general population improve their risk profile and survival.

It is also unknown, how CKD affects the differential epidemiology of cardiovascular diseases in immigrants, like if CKD influences the excess of stroke in SSA compared to the general population.

There is a clear gap in research analysing the outcome of renal transplantation in immigrants.

As depicted in this thesis, cultural aspects cannot be neglected as an important determinant of CKD in immigrants. More studies, also qualitative studies, are needed to analyse the intake of herbal medicine and the effect of diet and attitudes towards "Western" medicine, dialysis modality and transplantation on CKD.

There is a clear gap of knowledge on <u>health care utilisation</u> of immigrants with CKD, and those on dialysis or after transplantation. Utilisation is important in the context of CKD progression, timely referral to renal services before reaching ESRD, access to - and management and outcome after transplantation.

Over the counter purchase of <u>NSAIDs</u> may represent an important risk factor for CKD and CKD progression. How this affects CKD in the immigrant and the general population is not known.

5 Conclusions

- Renal diseases represent an important burden in immigrants in Europe.
- Available literature indicates a higher prevalence of <u>CKD</u>, as well as a faster progression with an increased ESRD incidence in the studied immigrant populations, as compared to the majority in Europe.
- In the context of <u>RRT</u>, studies point towards a lower mortality of immigrants on dialysis in Europe, as compared to the general population. There are only few studies on the outcome of renal transplantation in immigrants in Europe, and the results are conflicting.
- Reasons for this disparity, and particularly acculturation dynamics are insufficiently researched. The assessed determinants and mechanisms point towards multifactorial causes with an interplay of genetic risk variants, a higher prevalence of diabetes, hypertension and obesity, an increased risk of LBW, social deprivation (including SES, education and profession), culture shaped habits, beliefs and perceptions (by proxies like the use of traditional medicine, dietary habits and perception of body sizes), and also access to health care, especially primary care services.
- <u>Migration</u> influences renal health by intersecting with all of these determinants during the pre-migration phase, during transit, and upon arrival in the host country, and is thus a major determinant of the increased burden of CKD in immigrants in Europe.
- <u>LBW</u> is more common in LMIC and socially deprived populations, also in immigrants, and may therefore play a crucial role in linking social disadvantage leading to CKD in immigrants and possibly also in their offspring.
- The apparent <u>survival advantage</u> of immigrants on dialysis demands more research. It may be affected by selection, survival of relatively healthy individuals, return migration, and possibly favourable cardiovascular conditions.
- Further research is needed to understand the underlying mechanisms of the disparity of renal disease in immigrants in Europe. Findings could help to improve the health state of the whole populations at risk, and help to advance the evidence to appropriate policymaking.

6 Recommendations

1) Immigrants constitute a substantial part of the European population and immigrant´s health has to be a <u>priority on the agenda</u> of health ministries and public health policy makers. There is a need for a systematic data collection and monitoring of health of all immigrants using common definitions and migration indicators.

2) CKD should be acknowledged as a disease with a high burden in immigrants and as a relevant area of research in these populations. CKD is not merely a complication of diabetes and hypertension, but an own entity with complex causes and mechanism leading to high morbidity with impaired life quality, increased mortality and costs. With their extensive health and population registries, including the "Norwegian Renal Registry", Norway has a particular potential to conduct population-based studies on immigrants and renal health.

3) <u>International collaborations</u> are needed to facilitate collection of pre-migration health state data and variables like LBW or PE rates in the country of origin, and to compare the migrated populations to the non-migrated peers.

4) There is a need for more efforts on <u>identification of social, biological and genetic determinants</u> as a reason for the renal health disparity in immigrants in Europe. Studies on genetics or expression patterns of renal biopsies can help finding specific pathways and biomarkers related to increased CKD risk in particular groups. Social determinant include also addressing common factors like SES, and cultural aspects, like the use of traditional medicine. A qualitative approach is required to assess different beliefs and attitudes.

5) It is recommended to analyse the effect of LBW in CKD in immigrants in Europe and thus apply a "life course approach" including addressing pregnancy complications and outcomes in the context of renal disease later in life. This approach also includes acculturation dynamics, like duration of stay and other integration indicators, that are crucial for the immigrant's health and that always need to be considered. Offspring of immigrants may also be affected by renal disease and further research is needed on this population potentially at risk.

6) Ensuring healthy pregnancies and avoiding risk factors linked to PE and LBW need to be prioritised in general, and also in the context of improving renal health in immigrants in Europe.

7) Health care utilisation in the context of renal health and the effect on CKD progression and RRT outcomes in immigrants as compared to the majority have to be addressed and studied in detail.

8) Finally, the importance of a good physician-patient relationship should be further studied, emphasised and promoted, and training of all health care providers in cultural competence offered in medical schools, during and after specialisation.

7 References

1.   KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International,* 2013, 3(1):1-163
2.   Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One,* 2016, 11(7):e0158765
3.   Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet,* 2017, 390(10105):1888-917
4.   Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM. Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol,* 2008, 19(1):151-7
5.   Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med,* 2008, 359(8):800-9
6.   Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. *Lancet,* 2017, 389(10075):1238-52
7.   USRDS. United States Renal Data System. USRDS annual data report 2017: Epidemiology of kidney disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2017, https://www.usrds.org/adr.aspx
8.   Reisaeter AV. Annual Report 2016. The Norwegian Renal Registry (Norsk Nyreregister). Renal Unit, OUS-Rikshospitalet, Oslo, Norway, 2016, 1-14. http://www.nephro.no/registry.html
9.   Liu ZH. Nephrology in china. *Nat Rev Nephrol,* 2013, 9(9):523-8
10.   Maoujoud O, Aatif T, Bahadi A, Zajjari Y, Benyahya M, Ahid S, et al. Regional disparities in etiology of end-stage renal disease in Africa. *Saudi J Kidney Dis Transpl,* 2013, 24(3):594-5
11.   Tsai WC, Wu HY, Peng YS, Ko MJ, Wu MS, Hung KY, et al. Risk Factors for Development and Progression of Chronic Kidney Disease: A Systematic Review and Exploratory Meta-Analysis. *Medicine (Baltimore),* 2016, 95(11):e3013
12.   Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med,* 2004, 351(13):1296-305
13.   Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet,* 2013, 382(9888):260-72
14.   Gorodetskaya I, Zenios S, McCulloch CE, Bostrom A, Hsu CY, Bindman AB, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int,* 2005, 68(6):2801-8
15.   Vassalotti JA, Li S, McCullough PA, Bakris GL. Kidney early evaluation program: a community-based screening approach to address disparities in chronic kidney disease. *Semin Nephrol,* 2010, 30(1):66-73
16.   IOM (2019) International Organization for Migration. Glossary on migration. International migration law., Geneva, Switzerland1-248. 1813-2278
17.   Abubakar I, Aldridge RW, Devakumar D, Orcutt M, Burns R, Barreto ML, et al. The UCL-Lancet Commission on Migration and Health: the health of a world on the move. *Lancet,* 2018, 392(10164):2606-54
18.   Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, McKee M. Migration and health in an increasingly diverse Europe. *Lancet,* 2013, 381(9873):1235-45
19.   Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. *J Epidemiol Community Health,* 2004, 58(6):441-5
20.   IOM. International Organization for Migration. World migration report 2018. ISBN 978-92-9068-742-9, 2017, 1-364. ISBN 978-92-9068-742-9
21.   Eurostat. People in the EU - statistics on demographic changes. 2017. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=People_in_the_EU_-_statistics_on_demographic_changes - Foreigners_and_foreign-born_populations
22.   Eurostat. Eurostat: Migration and migrant population statistics. 2018. https://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics

23.   Raymer J. Migration in Europe. In White MJ (Ed.) International Handbook of Migration and Population Distribution. Springer. 2016,Vol. 6, 371-88. ISBN 978-94-017-7281-5

24.   BBC. Migrant crisis: Migration to Europe explained in seven charts. 2017. https://www.bbc.com/news/world-europe-34131911, 04.March 2016. Accessed on 25.07.2019.

25.   Parliament E. Asylum and migration in the EU: Facts and figures. 2017. http://www.europarl.europa.eu/news/en/headlines/society/20170629STO78630/asylum-and-migration-in-the-eu-facts-and-figures 30. June 2017. Accessed on 25.07.2019

26.   Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant,* 2017, 32(suppl_2):ii121-ii8

27.   GBD. Global Burden of Disease 2013 Mortality and Causes of Death Collaborators: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet,* 2015, 385(9963):117-71

28.   Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract,* 2017, 12840-50

29.   GBD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet,* 2017, 390(10100):1151-210

30.   Stanifer JW, Muiru A, Jafar TH, Patel UD. Chronic kidney disease in low- and middle-income countries. *Nephrol Dial Transplant,* 2016, 31(6):868-74

31.   Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Background document to WHO - Strategy paper. *Institute for Future studies,* 1991, 1-67

32.   Kumar BN, Diaz E (2019) Migrant Health: A primary care perspective., 306 9781138498044

33.   Aldridge RW, Nellums LB, Bartlett S, Barr AL, Patel P, Burns R, et al. Global patterns of mortality in international migrants: a systematic review and meta-analysis. *Lancet,* 2018, 392(10164):2553-66

34.   Norredam M, Agyemang C, Hoejbjerg Hansen OK, Petersen JH, Byberg S, Krasnik A, et al. Duration of residence and disease occurrence among refugees and family reunited immigrants: test of the 'healthy migrant effect' hypothesis. *Trop Med Int Health,* 2014, 19(8):958-67

35.   Syse A, Dzamarija MT, Kumar BN, Diaz E. An observational study of immigrant mortality differences in Norway by reason for migration, length of stay and characteristics of sending countries. *BMC Public Health,* 2018, 18(1):508

36.   Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. *Eur J Cancer,* 2010, 46(14):2647-59

37.   Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. *Adv Chronic Kidney Dis,* 2015, 22(1):6-15

38.   Morton RL, Schlackow I, Mihaylova B, Staplin ND, Gray A, Cass A. The impact of social disadvantage in moderate-to-severe chronic kidney disease: an equity-focused systematic review. *Nephrol Dial Transplant,* 2016, 31(1):46-56

39.   Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol,* 2009, 62(10):1006-12

40.   Burden AC, McNally PG, Feehally J, Walls J. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. *Diabet Med,* 1992, 9(7):641-5

41.   Lightstone L, Rees AJ, Tomson C, Walls J, Winearls CG, Feehally J. High incidence of end-stage renal disease in Indo-Asians in the UK. *QJM,* 1995, 88(3):191-5

42.   Higgins RM, Edmunds ME, Dukes DC. End-stage renal failure in Indo-Asians. *QJM,* 1995, 88(7):523-4

43.   Koppiker N, Feehally J, Raymond N, Abrams KR, Burden AC. Rate of decline in renal function in Indo-Asians and Whites with diabetic nephropathy. *Diabet Med,* 1998, 15(1):60-5

44.   Earle KK, Porter KA, Ostberg J, Yudkin JS. Variation in the progression of diabetic nephropathy according to racial origin. *Nephrol Dial Transplant,* 2001, 16(2):286-90

45.   Dreyer G, Hull S, Aitken Z, Chesser A, Yaqoob MM. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. *QJM,* 2009, 102(4):261-9

46.   Hull S, Dreyer G, Badrick E, Chesser A, Yaqoob MM. The relationship of ethnicity to the prevalence and management of hypertension and associated chronic kidney disease. *BMC Nephrol,* 2011, 1241

47.   Dreyer G, Hull S, Mathur R, Chesser A, Yaqoob MM. Progression of chronic kidney disease in a multi-ethnic community cohort of patients with diabetes mellitus. *Diabet Med,* 2013, 30(8):956-63

48.   Ali O, Mohiuddin A, Mathur R, Dreyer G, Hull S, Yaqoob MM. A cohort study on the rate of progression of diabetic chronic kidney disease in different ethnic groups. *BMJ Open,* 2013, 3(2):50-55

49.   Khunti K, Morris DH, Weston CL, Gray LJ, Webb DR, Davies MJ. Joint prevalence of diabetes, impaired glucose regulation, cardiovascular disease risk and chronic kidney disease in South Asians and White Europeans. *PLoS One,* 2013, 8(1):e55580

50.   Pallayova M, Rayner H, Taheri S, Dasgupta I. Is there a difference in progression of renal disease between South Asian and white European diabetic adults with moderately reduced kidney function? *J Diabetes Complications,* 2015, 29(6):761-5

51.   Mathur R, Dreyer G, Yaqoob MM, Hull SA. Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study. *BMJ Open,* 2018, 8(3):e020145

52.   Major R, Shepherd D, Gang X, Medcalf J, Gray L, Brunskill N. Co-morbidities and outcomes in South Asian individuals with chronic kidney diseas compared to white ethnicities. *Nephrol Dial Transplant,* 2019, 34(Supplement_1):p.gfz106

53.   Chandie Shaw PK, Vandenbroucke JP, Tjandra YI, Rosendaal FR, Rosman JB, Geerlings W, et al. Increased end-stage diabetic nephropathy in Indo-Asian immigrants living in the Netherlands. *Diabetologia,* 2002, 45(3):337-41

54.   Wandell P, Carlsson AC, Li X, Gasevic D, Arnlov J, Sundquist J, et al. End-Stage Kidney Diseases in Immigrant Groups: A Nationwide Cohort Study in Sweden. *Am J Nephrol,* 2019, 49(3):186-92

55.   van den Beukel TO, de Goeij MC, Dekker FW, Siegert CE, Halbesma N, Group PS. Differences in progression to ESRD between black and white patients receiving predialysis care in a universal health care system. *Clin J Am Soc Nephrol,* 2013, 8(9):1540-7

56.   Agyemang C, Snijder MB, Adjei DN, van den Born BJ, Modesti PA, Peters RJ, et al. Ethnic Disparities in CKD in the Netherlands: The Healthy Life in an Urban Setting (HELIUS) Study. *Am J Kidney Dis,* 2016, 67(3):391-9

57.   Adjei DN, Stronks K, Adu D, Beune E, Meeks K, Smeeth L, et al. Chronic kidney disease burden among African migrants in three European countries and in urban and rural Ghana: the RODAM cross-sectional study. *Nephrol Dial Transplant,* 2018, 33(10):1812-22

58.   Choukem SP, Fabreguettes C, Akwo E, Porcher R, Nguewa JL, Bouche C, et al. Influence of migration on characteristics of type 2 diabetes in sub-Saharan Africans. *Diabetes Metab,* 2014, 40(1):56-60

59.   Roderick PJ, Raleigh VS, Hallam L, Mallick NP. The need and demand for renal replacement therapy in ethnic minorities in England. *J Epidemiol Community Health,* 1996, 50(3):334-9

60.   Roodnat JI, Zietse R, Rischen-Vos J, van Gelder T, Mulder PG, JN IJ, et al. Effect of race on kidney transplant survival in non-European recipients. *Transplant Proc,* 1999, 31(1-2):312-3

61.   Frassinetti Fernandes P, Ellis PA, Roderick PJ, Cairns HS, Hicks JA, Cameron JS. Causes of end-stage renal failure in black patients starting renal replacement therapy. *Am J Kidney Dis,* 2000, 36(2):301-9

62.   Jeffrey RF, Woodrow G, Mahler J, Johnson R, Newstead CG. Indo-Asian experience of renal transplantation in Yorkshire: results of a 10-year survey. *Transplantation,* 2002, 73(10):1652-7

63.   Prasad S, Singh S, Duncan N, Cairns TD, Griffith M, Hakim N, et al. Ethnicity and survival on dialysis in west London. *Kidney Int,* 2004, 66(6):2416-21

64.   Pallet N, Thervet E, Alberti C, Emal-Aglae V, Bedrossian J, Martinez F, et al. Kidney transplant in black recipients: are African Europeans different from African Americans? *Am J Transplant,* 2005, 5(11):2682-7

65.   Lambie M, Richards N, Smith S. Ethnicity, age and incidence rates for renal replacement therapy (RRT) in Birmingham, UK: 1990-2004. *Nephrol Dial Transplant,* 2008, 23(12):3983-7

66.   van den Beukel TO, Dekker FW, Siegert CE. Increased survival of immigrant compared to native dialysis patients in an urban setting in the Netherlands. *Nephrol Dial Transplant,* 2008, 23(11):3571-7

67.   Merida E, Rodriguez A, Hernandez G, Huerta A, Gonzalez J, Hernandez A, et al. Renal transplantation in emigrants from Africa in Spain: similar results but different infectious profile compared with Spanish people. *Transplant Proc,* 2009, 41(6):2363-5

68.   Roderick P, Byrne C, Casula A, Steenkamp R, Ansell D, Burden R, et al. Survival of patients from South Asian and Black populations starting renal replacement therapy in England and Wales. *Nephrol Dial Transplant,* 2009, 24(12):3774-82

69.   Judge A, Caskey FJ, Welton NJ, Ansell D, Tomson CR, Roderick PJ, et al. Inequalities in rates of renal replacement therapy in England: does it matter who you are or where you live? *Nephrol Dial Transplant,* 2012, 27(4):1598-607

70.   Fotheringham J, Jacques RM, Fogarty D, Tomson CR, El Nahas M, Campbell MJ. Variation in centre-specific survival in patients starting renal replacement therapy in England is explained by enhanced comorbidity information from hospitalization data. *Nephrol Dial Transplant,* 2014, 29(2):422-30

71.   Cole N, Bedford M, Cai A, Jones C, Cairns H, Jayawardene S. Black ethnicity predicts better survival on dialysis despite greater deprivation and co-morbidity: a UK study. *Clin Nephrol,* 2014, 82(2):77-82

72.   van den Beukel TO, Hommel K, Kamper AL, Heaf JG, Siegert CE, Honig A, et al. Differences in survival on chronic dialysis treatment between ethnic groups in Denmark: a population-wide, national cohort study. *Nephrol Dial Transplant,* 2016, 31(7):1160-7

73.   Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science,* 2010, 329(5993):841-5

74.   Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol,* 2011, 22(11):2098-105

75.   Cooke JN, Bostrom MA, Hicks PJ, Ng MC, Hellwege JN, Comeau ME, et al. Polymorphisms in MYH9 are associated with diabetic nephropathy in European Americans. *Nephrol Dial Transplant,* 2012, 27(4):1505-11

76.   Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med,* 2013, 369(23):2183-96

77.   O'Seaghdha CM, Parekh RS, Hwang SJ, Li M, Kottgen A, Coresh J, et al. The MYH9/APOL1 region and chronic kidney disease in European-Americans. *Hum Mol Genet,* 2011, 20(12):2450-6

78.   McKnight AJ, Duffy S, Fogarty DG, Maxwell AP. Association of MYH9/APOL1 with chronic kidney disease in a UK population. *Nephrol Dial Transplant,* 2012, 27(9):3660; author reply 660-1

79.   Taber DJ, Su Z, Fleming JN, McGillicuddy JW, Posadas-Salas MA, Treiber FA, et al. Tacrolimus Trough Concentration Variability and Disparities in African American Kidney Transplantation. *Transplantation,* 2017, 101(12):2931-8

80.   Meeks KA, Freitas-Da-Silva D, Adeyemo A, Beune EJ, Modesti PA, Stronks K, et al. Disparities in type 2 diabetes prevalence among ethnic minority groups resident in Europe: a systematic review and meta-analysis. *Intern Emerg Med,* 2016, 11(3):327-40

81.   Tran AT, Diep LM, Cooper JG, Claudi T, Straand J, Birkeland K, et al. Quality of care for patients with type 2 diabetes in general practice according to patients' ethnic background: a cross-sectional study from Oslo, Norway. *BMC Health Serv Res,* 2010, 10145

82.   Sundquist K, Chaikiat A, Leon VR, Johansson SE, Sundquist J. Country of birth, socioeconomic factors, and risk factor control in patients with type 2 diabetes: a Swedish study from 25 primary health-care centres. *Diabetes Metab Res Rev,* 2011, 27(3):244-54

83. Andersen GS, Kamper-Jorgensen Z, Carstensen B, Norredam M, Bygbjerg IC, Jorgensen ME. Diabetes among migrants in Denmark: Incidence, mortality, and prevalence based on a longitudinal register study of the entire Danish population. *Diabetes Res Clin Pract,* 2016, 1229-16

84. Kristensen JK, Bak JF, Wittrup I, Lauritzen T. Diabetes prevalence and quality of diabetes care among Lebanese or Turkish immigrants compared to a native Danish population. *Prim Care Diabetes,* 2007, 1(3):159-65

85. Agyemang C, Kieft S, Snijder MB, Beune EJ, van den Born BJ, Brewster LM, et al. Hypertension control in a large multi-ethnic cohort in Amsterdam, The Netherlands: the HELIUS study. *Int J Cardiol,* 2015, 183180-9

86. El-Sayed AM, Scarborough P, Galea S. Ethnic inequalities in obesity among children and adults in the UK: a systematic review of the literature. *Obes Rev,* 2011, 12(5):e516-34

87. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health,* 2019, 7(7):e849-e60

88. Bollini P, Pampallona S, Wanner P, Kupelnick B. Pregnancy outcome of migrant women and integration policy: a systematic review of the international literature. *Soc Sci Med,* 2009, 68(3):452-61

89. Kelly Y, Panico L, Bartley M, Marmot M, Nazroo J, Sacker A. Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. *J Public Health (Oxf),* 2009, 31(1):131-7

90. Juarez SP, Revuelta-Eugercios BA. Exploring the 'Healthy Migrant Paradox' in Sweden. A Cross Sectional Study Focused on Perinatal Outcomes. *J Immigr Minor Health,* 2016, 18(1):42-50

91. Racape J, Schoenborn C, Sow M, Alexander S, De Spiegelaere M. Are all immigrant mothers really at risk of low birth weight and perinatal mortality? The crucial role of socio-economic status. *BMC Pregnancy Childbirth,* 2016, 1675

92. Urquia ML, Glazier RH, Gagnon AJ, Mortensen LH, Nybo Andersen AM, Janevic T, et al. Disparities in pre-eclampsia and eclampsia among immigrant women giving birth in six industrialised countries. *BJOG,* 2014, 121(12):1492-500

93. Naimy Z, Grytten J, Monkerud L, Eskild A. The prevalence of pre-eclampsia in migrant relative to native Norwegian women: a population-based study. *BJOG,* 2015, 122(6):859-65

94. Nilsen RM, Vik ES, Rasmussen SA, Small R, Moster D, Schytt E, et al. Preeclampsia by maternal reasons for immigration: a population-based study. *BMC Pregnancy Childbirth,* 2018, 18(1):423

95. Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. *Nat Rev Nephrol,* 2012, 8(9):533-41

96. Merkin SS, Diez Roux AV, Coresh J, Fried LF, Jackson SA, Powe NR. Individual and neighborhood socioeconomic status and progressive chronic kidney disease in an elderly population: The Cardiovascular Health Study. *Soc Sci Med,* 2007, 65(4):809-21

97. Bello AK, Peters J, Rigby J, Rahman AA, El Nahas M. Socioeconomic status and chronic kidney disease at presentation to a renal service in the United Kingdom. *Clin J Am Soc Nephrol,* 2008, 3(5):1316-23

98. Caskey FJ. Renal replacement therapy: can we separate the effects of social deprivation and ethnicity? *Kidney Int Suppl (2011),* 2013, 3(2):246-9

99. Vart P, Gansevoort RT, Coresh J, Reijneveld SA, Bultmann U. Socioeconomic measures and CKD in the United States and The Netherlands. *Clin J Am Soc Nephrol,* 2013, 8(10):1685-93

100. Adjei DN, Stronks K, Adu D, Snijder MB, Modesti PA, Peters RJG, et al. Relationship between educational and occupational levels, and Chronic Kidney Disease in a multi-ethnic sample- The HELIUS study. *PLoS One,* 2017, 12(11):e0186460

101. van Andel T, Westers P. Why Surinamese migrants in the Netherlands continue to use medicinal herbs from their home country. *J Ethnopharmacol,* 2010, 127(3):694-701

102. Beune EJ, Haafkens JA, Agyemang C, Schuster JS, Willems DL. How Ghanaian, African-Surinamese and Dutch patients perceive and manage antihypertensive drug treatment: a qualitative study. *J Hypertens,* 2008, 26(4):648-56

103.   de Brito-Ashurst I, Perry L, Sanders TA, Thomas JE, Yaqoob MM, Dobbie H. Barriers and facilitators of dietary sodium restriction amongst Bangladeshi chronic kidney disease patients. *J Hum Nutr Diet,* 2011, 24(1):86-95

104.   Toselli S, Rinaldo N, Gualdi-Russo E. Body image perception of African immigrants in Europe. *Global Health,* 2016, 12(1):48

105.   Summers DM, Johnson RJ, Hudson AJ, Collett D, Murphy P, Watson CJ, et al. Standardized deceased donor kidney donation rates in the UK reveal marked regional variation and highlight the potential for increasing kidney donation: a prospective cohort studydagger. *Br J Anaesth,* 2014, 113(1):83-90

106.   Rios A, Carrillo J, Lopez-Navas AI, Ayala MA, Garrido G, Sebastian MJ, et al. Nigerian Immigrant Population in Spain Is Little Sensitized to Living-Related Kidney Donation. *Transplant Proc,* 2018, 50(2):354-7

107.   Rios A, Lopez-Navas AI, Sanchez A, Ayala MA, Garrido G, Sebastian MJ, et al. Does the Attitude Toward Organ Donation Change as a Function of the Country Where People Emigrate? Study Between Uruguayan Emigrants to the United States and Spain. *Transplant Proc,* 2018, 50(2):334-7

108.   Bakewell AB, Higgins RM, Edmunds ME. Does ethnicity influence perceived quality of life of patients on dialysis and following renal transplant? *Nephrol Dial Transplant,* 2001, 16(7):1395-401

109.   Brathwaite R, Addo J, Kunst AE, Agyemang C, Owusu-Dabo E, de-Graft Aikins A, et al. Smoking prevalence differs by location of residence among Ghanaians in Africa and Europe: The RODAM study. *PLoS One,* 2017, 12(5):e0177291

110.   Agyemang C, Meeks K, Beune E, Owusu-Dabo E, Mockenhaupt FP, Addo J, et al. Obesity and type 2 diabetes in sub-Saharan Africans - Is the burden in today's Africa similar to African migrants in Europe? The RODAM study. *BMC Med,* 2016, 14(1):166

111.   Agyemang C, Nyaaba G, Beune E, Meeks K, Owusu-Dabo E, Addo J, et al. Variations in hypertension awareness, treatment, and control among Ghanaian migrants living in Amsterdam, Berlin, London, and nonmigrant Ghanaians living in rural and urban Ghana - the RODAM study. *J Hypertens,* 2018, 36(1):169-77

112.   Addo J, Agyemang C, de-Graft Aikins A, Beune E, Schulze MB, Danquah I, et al. Association between socioeconomic position and the prevalence of type 2 diabetes in Ghanaians in different geographic locations: the RODAM study. *J Epidemiol Community Health,* 2017, 71(7):633-9

113.   Sanou D, O'Reilly E, Ngnie-Teta I, Batal M, Mondain N, Andrew C, et al. Acculturation and nutritional health of immigrants in Canada: a scoping review. *J Immigr Minor Health,* 2014, 16(1):24-34

114.   Steffen PR, Smith TB, Larson M, Butler L. Acculturation to Western society as a risk factor for high blood pressure: a meta-analytic review. *Psychosom Med,* 2006, 68(3):386-97

115.   Sarria-Santamera A, Hijas-Gomez AI, Carmona R, Gimeno-Feliu LA. A systematic review of the use of health services by immigrants and native populations. *Public Health Rev,* 2016, 3728

116.   Diaz E, Kumar BN. Differential utilization of primary health care services among older immigrants and Norwegians: a register-based comparative study in Norway. *BMC Health Serv Res,* 2014, 14623

117.   Cass A, Cunningham J, Snelling P, Ayanian JZ. Late referral to a nephrologist reduces access to renal transplantation. *Am J Kidney Dis,* 2003, 42(5):1043-9

118.   Udayaraj U, Ben-Shlomo Y, Roderick P, Casula A, Dudley C, Johnson R, et al. Social deprivation, ethnicity, and access to the deceased donor kidney transplant waiting list in England and Wales. *Transplantation,* 2010, 90(3):279-85

119.   Hull S, Mathur R, Dreyer G, Yaqoob MM. Evaluating ethnic differences in the prescription of NSAIDs for chronic kidney disease: a cross-sectional survey of patients in general practice. *Br J Gen Pract,* 2014, 64(624):e448-55

120.   Hunt LM, Schneider S, Comer B. Should "acculturation" be a variable in health research? A critical review of research on US Hispanics. *Soc Sci Med,* 2004, 59(5):973-86

121.   Fox M, Thayer Z, Wadhwa PD. Assessment of acculturation in minority health research. *Soc Sci Med,* 2017, 176123-32

122.   Rayner HC, Pisoni RL, Bommer J, Canaud B, Hecking E, Locatelli F, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the

Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant,* 2004, 19(1):108-20

123. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health,* 2014, 2(3):e174-81

124. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. *Am J Clin Nutr,* 2006, 84(2):289-98

125. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull,* 2001, 605-20

126. Lackland DT, Egan BM, Fan ZJ, Syddall HE. Low birth weight contributes to the excess prevalence of end-stage renal disease in African Americans. *J Clin Hypertens (Greenwich),* 2001, 3(1):29-31

127. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet,* 2012, 379(9832):2162-72

128. Garcia-Garcia G, Jha V. CKD in disadvantaged populations. *Arch Iran Med,* 2015, 18(3):206-9

129. Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. *Eur Heart J,* 2000, 21(14):1141-51

130. Holdsworth M, Gartner A, Landais E, Maire B, Delpeuch F. Perceptions of healthy and desirable body size in urban Senegalese women. *Int J Obes Relat Metab Disord,* 2004, 28(12):1561-8

131. Puoane T, Tsolekile L, Steyn N. Perceptions about body image and sizes among Black African girls living in Cape Town. *Ethn Dis,* 2010, 20(1):29-34

132. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: Systematic review and meta-analysis. *PLoS One,* 2017, 12(5):e0177151

133. Rhee CM, Kalantar-Zadeh K, Norris KC. Why minorities live longer on dialysis: an in-depth examination of the Danish nephrology registry. *Nephrol Dial Transplant,* 2016, 31(7):1027-30

134. Agyemang C, Addo J, Bhopal R, Aikins Ade G, Stronks K. Cardiovascular disease, diabetes and established risk factors among populations of sub-Saharan African descent in Europe: a literature review. *Global Health,* 2009, 57

135. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol,* 2006, 17(8):2275-84

136. Agyemang C, Bhopal RS. Is the blood pressure of South Asian adults in the UK higher or lower than that in European white adults? A review of cross-sectional data. *J Hum Hypertens,* 2002, 16(11):739-51

137. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, et al. Race, APOL1 Risk, and eGFR Decline in the General Population. *J Am Soc Nephrol,* 2016, 27(9):2842-50

138. Kumar BN, Meyer HE, Wandel M, Dalen I, Holmboe-Ottesen G. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. *Int J Obes (Lond),* 2006, 30(4):684-90

139. Urquia ML, Glazier RH, Blondel B, Zeitlin J, Gissler M, Macfarlane A, et al. International migration and adverse birth outcomes: role of ethnicity, region of origin and destination. *J Epidemiol Community Health,* 2010, 64(3):243-51

140. Jha V, Rathi M. Natural medicines causing acute kidney injury. *Semin Nephrol,* 2008, 28(4):416-28

8 Annexes

Table A1: *Included articles on chronic kidney disease in immigrants in Europe[1]*

Reference	Study population	Study method Comparison group	Outcome measure	Major findings
(Burden et al., 1992) (40)	Asian in UK	Cohort study, follow-up of 9 years. Comparison group: White UK resident. Total of 379 patients with and without diabetes	- ESRD incidence	- Incidence of ESRD due to other causes than diabetes was higher in Asian (RR 14) - Incidence of ESRD due to diabetes mellitus was higher in Asian (RR 3.7).
(Lightstone et al, 1995) (41)	Indo-Asians in UK	Cross-sectional study. Comparison group: White UK residents. Total of 447 patients started on RRT.	- ESRD cause - ESRD incidence	- More infectious diseases and glomerulonephritis in Asians as compared to White UK residents. - 5 times higher rate of ESRD from unknown cause in Asians - 3-5-fold higher incidence of ESRD in the Asian population
(Higgins et al., 1995) (42)	Indo-Asians and Afro-Caribbean in UK	Cross-sectional study. Comparison group: White UK residents. Total of 106 patients started in on dialysis.	- ESRD incidence	- nearly 10-fold higher incidence of ESRD in the Indo-Asian/Afro-Caribbean group.
(Koppiker et al., 1998) (43)	Indo-Asians living in Leicester, UK.	Cohort study, follow-up 16-30 months. Comparison group: White UK residents. Total of 39 patients with CKD 3-5 on the base of diabetic nephropathy.	- CKD progression (creatinine increase)	- Similar rate of creatinine increase in the groups.

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[1] The terminology of the study population of interest is consciously kept like the original article stated it.

(Earle et al., 2001) (44)	Blacks and Indo-Asians living in London, UK.	Cohort study, follow-up of 37-46 months Comparison group: White UK residents. <u>Total of 45 patients</u> with CKD 3-5 on the ground of diabetic nephropathy.	- CKD progression (doubling of serum-creatinine)	- Higher risk of CKD progression in Indo-Asians.
(Dreyer et al., 2009) (45)	South Asians, Blacks and Whites living in London UK.	Cross-sectional study. <u>Comparison group</u>: White UK patients. <u>Total 34'359</u> patients with diabetes mellitus.	- CKD prevalence	- Lower prevalence of CKD3 in SA and Blacks. - Higher prevalence of CKD4-5 in SA (OR 1.5) and Blacks (OR 1.4). - Higher prevalence of DM2 in SA and Blacks compared to Whites
(Hull et al., 2011) (46)	South Asians and Blacks in UK.	Cross-sectional study. <u>Comparison group</u>: White UK residents. <u>Total of 49'203 patients</u> with hypertension.	- CKD prevalence (MDRD)	- Same CKD3 prevalence in Blacks and Whites. - Less CKD3 in SA. - Higher CKD 4-5 prevalence in SA group compared to White and Black group.
(Dreyer et al., 2013) (47)	South Asians, Blacks and Whites living in London UK.	Cohort study, follow-up mean 5 years. <u>Comparison group</u>: White UK patients. <u>Total 3855</u> patients with diabetes mellitus.	- CKD progression (MDRD)	- Faster decline of renal function in SA compared to Whites. - In patients with proteinuria, the decline was faster in SA and Blacks as compared to Whites.
(Ali et al., 2013) (48)	South Asians, Blacks and Whites living in London UK.	Cohort study, follow-up mean 6 years. <u>Comparison group</u>: White UK patients with CKD. <u>Total 329</u> patients with biopsy proven diabetic nephropathy and CKD.	- CKD progression (MDRD) - ESRD incidence - Mortality	- No significant difference in annual eGFR decline between different ethnic groups. - No difference in ESRD incidence or mortality.

(Khunti et al., 2013) (49)	South Asians and White UK residents.	Cross-sectional study (ADDITION-Leicester study) Comparison group: White UK individuals. Total 3707 patients eligible for a UK-NHS cardiovascular screening programme.	- CKD prevalence (eGFR, MDRD)	- Lower CKD prevalence in SA compared to Whites.
(Pallayova et al., 2015) (50)	South Asian in UK.	Cross-sectional study. Comparison group: White UK residents. Total 1173 patients with diabetes and CKD3.	- CKD progression (MDRD)	- SA and Whites have similar rates of CKD progression.
(Mathur et al, 2018) (51)	South Asian, Black and White population living in East London, UK.	Cohort study, follow-up mean 9 years. Comparison group: White UK patients. Total 6274 patients with DM2 and CKD.	- CKD progression (MDRD) - ESRD incidence - Mortality	- CKD progression fastest in Blacks and in Bangladeshi. - Highest ESRD risk in Blacks compared to Whites (HR of 2.23). - Lower mortality in SA group compared to Whites, especially in Bangladeshi.
(Major et al., 2019) (52)	South Asians living in UK.	Cohort study, follow-up 5 years. Comparison group: White UK residents. Total of 17'248 patients with CKD 3-4.	- ESRD incidence - Mortality	- Higher incidence of ESRD in South-Asians (HR 1.6) - Lower mortality (HR 0.75) compared to the white population.
(Chandie Shaw et al., 2002) (53)	Immigrants from Suriname and White Dutch living in the Hague, NL.	Case-control study. Comparison group: White Dutch individuals. Total 56 patients with DM2 on dialysis due to diabetic nephropathy.	- ESRD incidence	- 40 times increased risk for ESRD in immigrants from Surinam compared to White Dutch, all with DM2.

(Van den Beukel et al., 2013) (55)	Blacks in NL.	Multi-center cohort study, PREPARE (Pre-dialysis patient record study). Follow-up mean 13 months Comparison group: White Dutch. Total of 1049 patients with CKD4-5.	- CKD progression (MDRD) - RRT incidence	- Higher RRT incidence in Blacks. - Blacks have higher eGFR when referred to the nephrology clinic. - Faster decline of eGFR in Blacks.
(Agyemang et al., 2016) (56)	South Asian, African Surinamese, Ghanaian, Turks, Moroccans and ethnic Dutch living in Amsterdam (origin participant and parents).	Cross-sectional study (HELIUS study (Healthy Life In an Urban Setting)). Comparison group: Ethnic Dutch. Total 12'800 patients, including 1st and 2nd-generation migrants.	- CKD prevalence (CKD-EPI) - Albuminuria	- Higher CKD prevalence in ethnic groups: 1.5 (African Surinamese) to 2.7-fold (Turks) higher prevalence. - Higher prevalence of albuminuria in ethnic groups
(Adjei et al., 2018) (57)	Ghanaian living in rural and urban Ghana and their migrated peers in Amsterdam, Berlin and London.	Multi-centre cross-sectional study RODAM (Research on obesity and diabetes among African Immigrants), multi-centre study. Comparison group: Migrated Ghanaian in Amsterdam, Berlin and London. No comparison to non-migrated Europeans. Total of 8131 Ghanaian.	- CKD prevalence (CKD-EPI)	- Higher CKD prevalence in non-migrated Ghanaian compared to migrated peers. - Higher CKD prevalence in non-migrated Ghanaian with hypertension and diabetes compared to migrated peers. - Lower CKD prevalence in rural compared to urban Ghana. - Lower CKD prevalence in Amsterdam than in Berlin.
(Choukem et al., 2014) (58)	Sub-Saharan African living in France and Cameroonians living in urban Cameroun	Cross-sectional study. Comparison group: Caucasians living in France. Total of 397 patients with DM2.	- Prevalence of diabetic nephropathy	- No difference in prevalence of diabetic nephropathy between migrated Cameroonians and Caucasians in France - Higher prevalence of diabetic nephropathy in non-migrated Africans compared to migrated peers.

| (Wandell et al., 2019) (54) | All immigrants in Sweden. | Cohort study, follow-up 14 years. Register-based.

Comparison group: Second generation immigrants and Swedish population.
Total of 6'44'649 individuals in immigrant analysis. | - ESRD incidence (ICD-10 code) | - Higher ESRD incidence in first generation immigrants (HR 1.1), in particular in those from Easter Europe (Bosnia, Bulgaria), African, and Asian.
- Generally no higher incidence in "second generation "immigrants, though higher HR for ESRD in offspring with background from Netherlands, Bosnia, and Asia (Lebanon HR 2, Turkey 1.2, and "other Asian countries" HR 1.27 (0.94-2.2).
- Lower ESRD incidence in immigrants from Finnland |

Table A2: *Included articles on renal replacement therapy in immigrants in Europe*

Reference	Study population	Study method Comparison group	Outcome measure	Major findings
(Roderick et al., 1996) (59)	Blacks and Asians in UK.	Cross-sectional study. Comparison group: White UK residents. Total population registered in UK (Census 1991) with a total of 5901 patients started on RRT.	- RRT initiation rate	- Higher risk for RRT in the Asian (initiation rate 4.2) and Black (initiation rate 3.7) population as compared to White UK residents
(Frassinetti et al., 2000) (61)	Blacks living in UK.	Case-control study. Comparison group: White UK residents. Total of 288 patents of patients on RRT.	- ESRD cause	- Diabetes more common cause for ESRD in Blacks (OR 2.9) - More hypertension (OR 0.98-9.82) in Blacks. - No difference in glomerulonephritis. - Polycystic renal disease more common in Whites (OR 5). - No difference in time of referral.
(Prasad et al., 2004) (63)	Indo-Asians and Blacks living in London, UK	Cohort study, follow-up 5 years. Comparison group: White UK residents. Total of 474 patients that started with dialysis.	- Mortality on dialysis	- Higher prevalence of diabetes mellitus and thus higher cardiovascular risk in Indo-Asians and Blacks. - No difference of survival between groups.
(Lambie et al., 2008) (65)	Blacks and Indo-Asians in Birmingham, UK.	Cohort study, with two cohorts, follow-up each 5 years. Comparison group: White UK residents. Total population registered in Birmingham (Census 1991 966'041, census 2001 977'099) with a total of 1810 patients that started RRT	- RRT initiation rate	- Higher incidence of RRT in Indo-Asians (RR 1.88) or Blacks (RR 2.16). - The highest increase in RRT incidence in >70 year old Blacks or Indo-Asians.

(Roderick et al., 2009) (68)	South Asians and Blacks living in UK.	Cohort study, follow-up 1.8 years (median) Comparison group: white UK residents. Total of 30'561 patients on dialysis.	- Mortality on dialysis	- Lower mortality of SA (HR 0.7) and Blacks (HR 0.56).
(Judge et al., 2012) (69)	Blacks and South-Asians in UK.	Cross-sectional study. Comparison group: White UK residents. Total of 4609 patients on RRT. The denominator is not given.	- RRT initiation rate	RRT initiation rate is higher in the regions with the highest percentage of Black (initiation rate 1.92) or SA (initiation rate 1.73) population.
(Cole et al., 2014) (71)	Blacks living in UK	Cohort study, follow-up 5 years. Comparison group: White UK residents. Total of 1340 patients started on dialysis.	- ESRD cause - Mortality on dialysis	- Higher prevalence of diabetes and diabetic nephropathy as cause for ESRD in Blacks. - More hypertensive nephropathy in Blacks. - Lower mortality of Blacks compared to Whites (HR 0.51).
(Fotheringham et al., 2014) (70)	South Asians and Blacks in UK.	Cohort study, follow-up 31 months. Comparison group: White UK residents. Total of 18'798 patients on RRT.	- Mortality on dialysis - Comorbidity	- Lower mortality in SAs and blacks on dialysis. - Less comorbidities in Blacks - Similar number of comorbidities in SAs and Blacks
(Van den Beukel et al., 2008) (66)	Immigrants in NL.	Cohort study, follow-up 28-37 months. Comparison group: Dutch. Total of 303 patients that initiated HD or PD.	- Mortality on dialysis	- Higher mortality in Dutch patients compared to immigrants (RR 2.7. Controlled RR 1.9). - No difference in cause of death between groups.

(Van den Beukel et al., 2016) (72)	Immigrants in Denmark.	Cohort study, mean follow-up 23 months, data based on Danish Nephrology Registry Comparison groups: Danish individuals. Total of 9109 patients initiated on HD or PD.	- Mortality on dialysis	- Highest mortality in Danes compared to Western immigrants (HR 1.32), immigrants from North Africa or West Asia (2.22), South or South-East Asia (1.79) or SSA (2.0) - Survival benefit in Western immigrant becomes less over time, though not in non-Western immigrants.
(Jeffrey et al., 2002) (62)	Indo-Asian living in Yorkshire, UK.	Cohort study, follow-up 5 years. Comparison group: Non-Asian patients on dialysis. Total of 608 patients after transplantation.	Transplantation - Time to transplantation - Allograft survival rate - Mortality after transplantation	- Longer time to transplantation in Indo-Asians - Higher risk for loss of allograft in Indo-Asians (RR 1.55). - Mortality after transplantation was higher in Indo-Asians compared to non-Asians.
(Pallet et al., 2005) (64)	African residence in France (SSA and Caribbean origin)	Cohort study, follow-up 5 years Comparison group: White French residents. Total of 1092 patients who underwent transplantation.	- ESRD cause Transplantation: - Delayed allograft function - Rejection - Allograft function - Allograft survival rate - Mortality after transplantation	- More ESRD due to hypertension in Blacks. More polycystic renal disease in Caucasians - More delayed allograft function in Africans. - No difference in rejection - No difference in allograft survival. - No difference in mortality. - No difference in rate of HLA mismatch and hyperimmunity.
(Merida et al., 2009) (67)	African immigrants in Spain.	Cohort study, follow-up 68-76 months. Comparison group: Spanish residents. Total 76 patients after renal transplantation.	ESRD cause Transplantation: - Allograft function - Rejection - Mortality after transplantation	- More ESRD due to hypertension in African immigrants. More glomerulonephritis in Spanish. - No difference in rate of HLA mismatch and hyperimmunity. - Rejection and loss of allograft function more common in African - No difference in mortality after transplantation

| (Roodnat et al., 1999) (60) | African, Asian, Arabian and Turkish in NL. | Cohort study, follow-up at least 6 months.

Comparison group: European. Total of 805 patients receiving kidney transplantation. | Transplantation
- Allograft survival rate | - No difference in HLA mismatch
- No difference in allograft survival between European and non-European.
- Worse allograft survival in Arabian and African compared to Asian groups |

Table A3

Study population	Diabetic NP	Hypertensive NP	Glomerulo-nephritis	Chronic PN	Polycystic kidney	Other causes
SA (UK) (41, 59)	↑	=	↑	↑	↓	↑
Blacks (UK) (59, 61, 71)	↑	↑	↑=	↑=	↓	=
African immigrants (France) (64)	=	↑	=	↑	↓	
Blacks (NL) (55)	↑	=	↑			
African immigrants (Spain) (67)	↓	↑	↓	↑	↓	
Immigrants* (NL) (66)	=	=	↑	=	=	=
"Western", North African, SSA, West, East and SA in Denmark (72)	↑	=	↑			↑

*Table A3: Summary of causes of CKD and ESRD in immigrant populations in Europe. NP = Nephropathy. PN = Pyelonephritis. Polycystic kidney = Polycystic kidney disease. *Immigrants originated from sub-Saharan Africa, Morocco, Suriname, East-Asia, Turkey and European countries.*

Table A4: *Determinants and mechanisms of chronic kidney disease and renal replacement therapy in immigrants in Europe.*

Determinant	Reference	Findings	Mechanisms
Genetics	(Genovese et al., 2010) (73)	Comparing genome sequencing of African Americans with European Americans in the U.S. - Variants in the two APOL1 allels are linked to increased risk for hypertensive ESRD and FSGS in African Americans.	- APOL1 is a gene that codes the protein apolipoprotein 1, which is involved in epithelial and vascular integrity and the innate immune system. - "Renal risk variants" of APOL1 may alter the protein function and increase risk for renal diseases. The precise mechanism is not known
	(Friedman et al., 2011) (74)	Genome sequencing of African American and European American in the U.S. - Around 40% of African Americans have one, 15% have two APOL1 "renal risk variant". - No APOL1 "renal risk variants" in European Americans. - No relation of APOL1 to diabetic nephropathy. - 10-fold increased risk of non-diabetic ESRD	- "Renal risk variants" of APOL1 are supposed to confer a resistance to African Sleeping Sickness caused by Trypanosoma parasites. This may have been a survival advantage and a reason for preservation of these gene variants in individuals with African Ancestry.
	(Parsa et al., 2013) (76)	Sequencing of African American with CKD due to hypertension or diabetes in the U.S. - Strongly increased progression of CKD in Black patients with or without diabetes, irrespective of BP control.	
	(Grams et al., 2016) (137)	Cohort study over 25 years in African Americans and European Americans in the U.S. - Two "renal risk variants" were linked to increased risk to diabetes, hypertension and ESRD in African American as compared to African Americans without the variants and European Americans.	
	(O´Seaghdha et al, 2011) (77)	Identification of MYH9 and APOL1 variants in European Americans from the Framinghham study. - MYH9 variant is linked to increased prevalence of CKD in non-diabetic European Americans.	- MYH9 is closely located to APOL1. MYH9 is expressed in podocytes and mesangial cells of the glomeruli.

	(Cooke et al., 2012) (75)	Sequencing of DM2 and healthy patients. - 0.3% of genome of European Americans comprises APOL1 risk variants. - MYH9 variants are linked to diabetic nephropathy in European Americans with DM2.	- Variants of MYH9 may impair glomerular function.
	(McKnight et al., 2012) (78)	Identification of MYH9/APOL1 variants in the genome of patients with diabetic nephropathy and ESRD in UK. - No association of genetic variants with diabetic nephropathy or ESRD in UK.	
	(Taber et al., 2017) (79)	Pharmacokinetics of Tacrolimus in African Americans. Lower Tacrolimus concentrations in African Americans. - Higher variability of Tacrolimus concentrations within African Americans. - More CYP3A5*1 variants in African Americans that lead to faster metabolism of Tacrolimus. - Lower Tacrolimus concentrations are linked to more rejection.	- Tacrolimus is a main immunosuppressive drug after renal transplantation. Low concentrations can lead to allograft rejection. - Tacrolimus is metabolized by the cytochrome p450 3A5 in the liver.
Diabetes	(Meeks et al., 2015) (80)	Literature review with 20 studies on prevalence of DM2 in ethnic groups in Europe. - Highest relative prevalence of DM2 in SA (3-5-fold), in particular in Bangladeshi (OR 6.2), Pakistani (OR 5.4) and Indians (OR 4.1). - High prevalence in North Africans and individuals from Middle Eastern (2-4-fold), SSA (2-3-fold). - Of note, Bangladeshi have less obesity as compared to the host European population.	- Diabetes mellitus is together with hypertension one of the most common reasons for CKD worldwide. - Hypothesized mechanisms for the increased prevalence of DM2 are increased genetic susceptibility with insulin resistance, increased prevalence of obesity, dietary aspects with intake of high caloric food and lower SES.
	(Tran et al., 2010) (81)	Cross-sectional study on ethnic groups in Norway. - Ethnic groups (e.g. SA and Middle Eastern/North Africans) were younger at DM2 diagnosis. - Achievement of HbA1c was worse in ethnic groups. - More patients in ethnic groups had HbA1c > 9%	- HbA1c reflects the average glycemia of the past months. The higher the HbA1c, the worse the glycemia is controlled and the higher the risk for complications such as kidney diseases.

	(Sundquist et al., 2011) (82)	Cross-sectional study on ethnic groups in Sweden. - Low SES was linked to worse diabetes control with higher HbA1c. - Ethnic groups from Middle Eastern Regions had worse glyacemic control as compared to Swedish "	
	(Andersen et al., 2016) (83)	Cross-sectional study on all immigrants in Denmark. - 2.5-fold increased incidence of diabetes mellitus (not distinguished types) in SSA, Asian and Middle Eastern immigrants as compared to Danes. - Higher overall mortality in all the diabetic immigrants except in SSA as compared to Danes.	
	(Kristensen et al., 2007) (84)	Cross-sectional study on ethnic groups in Denmark. - Distinctly higher prevalence of DM2 in Turkish and Lebanese as compared to Danish. - Worse glycaemic control in ethnic groups as compared to Danish.	
Hypertension	(Hull et al., 2011) (46)	Cross-sectional study in UK. - Higher prevalence of hypertension in SA and Blacks in UK. - Hypertension control was more often reached in SA as compared to Whites. - Hypertension control was worse in Blacks as compared to Whites.	- Hypertension is together with diabetes mellitus one of the most common reasons for CKD worldwide. - Hypertensive related CKD and CKD progression can be reduced by antihypertensive treatment with a target BP of <140/90mmHg,
	(Agyemang et al. 2015) (85)	HELIUS study with Dutch, Ghanaian, African-Surinamese, South-Asian Surinamese, Turkish and Moroccan participants. - Higher prevalence of hypertension in all immigrants except female Moroccan. Highest prevalence in Ghanaian men (3-4-fold), African Surinamese men (2-3-fold), SA Surinamese men (around 2-fold), Turkish men (1.5-2-fold) and Moroccan men (1-1.5-fold). - Worse BP control in all ethnic groups except Moroccans and Turkish as compared to Dutch - despite high awareness and treatment prevalence.	

Obesity	(Kumar et al., 2006) (138)	Cross-sectional study performed in Oslo, Norway. - Highest prevalence of obesity in Turkish people, in particular in women. - Highest abdominal circumference in people from Sri Lanka and Pakistan.	- Obesity, as defined as a BMI > 30mg/m2, is linked to increased cardiovascular risk, insulin resistance, risk for DM2, hypertension and renal diseases. - Abdominal obesity is in particular linked to cardiovascular risk.
	(El-Sayed et al., 2011) (86)	Literature review on the prevalence of obesity in ethnic groups in UK. - Studies on obesity in SA are ambivalent with some pointing towards more and some towards less obesity as compared to Whites. - Blacks in UK seem to have a higher prevalence of obesity as compared to Whites in this literature review.	
Low birth weight (LBW)	(Vikse et al., 2008) (4)	Population-based cohort study on the Norwegian population. - Low birth weight (<90 percentile) was associated with a 70% increased risk for ESRD later in life. - High birth weight (>4.5kg) was also associated with increased risk for ESRD.	- LBW can be defined as < 2.5kg birth weight irrespective of the duration of pregnancy - Kidney development during pregnancy undergoes different stages. The third trimester is thought to be crucial for development of the nephrons, the main "filtering unit" of the kidney. - Troubles during the third trimester, such as growth restriction, low birth weight or preterm birth, is thought to lead to less nephrons and lower "nephron reserve" and therefore higher risk of ESRD. - Kidney development during pregnancy undergoes different stages. The third trimester is thought to be crucial for development of the nephrons, the main "filtering unit" of the kidney.
	(Blencowe et al., 2019) (87)	Meta-analysis and global estimation of LBW prevalence between 2000 and 2005. - There is a global prevalence of 14.6% LBW. This is nearly 3 percent less than in 2000. Highest prevalence is noted in SA and in SSA.	
	(Bollini et al., 2008) (88)	Literature review on child and maternal perinatal morbidity - Immigrant mothers have a 40% increased risk for low birth weight children worldwide. - Relatively better outcomes in countries with pro-active integration programs such as Belgium, Sweden, Norway and NL.	

	(Juarez et al., 2016) (90)	Cross-sectional studies on immigrants and the host population in Sweden. - Immigrants in Sweden have a higher risk of LBW as compared to Swedish, in particular immigrants from South Asia (OR 2) and Africa (OR 1.5).	- Troubles during the third trimester, such as growth restriction, low birth weight or preterm birth, is thought to lead to less nephrons and lower "nephron reserve" and therefore higher risk of ESRD.
	(Kelly et al., 2008) (89)	Cross-sectional study on ethnic groups in UK - Higher prevalence of LBW in all ethnic groups of this study (Indian 2.4-fold, Pakistani 2.5-fold, Bangladeshi 2.2-fold, Black Caribbean 1.7-fold, Black African 1.7-fold)	- Many immigrant subgroups have a higher risk for LBW in their offspring as compared to the majority
	(Urquia et al., 2010) (139)	Metaanalysis on the prevalence and risk of LBW in different immigrant subgroups in the US and in Europe. - The risk for LBW depends on the country of birth and the host country: In the US, immigrants with African ancestry had less LBW children as compared to African Americans. Similarly, immigrant Hispanics had less LBW than US born Hispanics. - In Europe, immigrants with African ancestry had a higher risk for LBW as compared to the European women (OR 1.8) - SA immigrants had a higher risk of LBW in US (OR 1.3) and Europe (1.8) as compared to the US or European born population.	
	(Racape et al., 2016) (91)	Cross-sectional study on immigrants in Belgium - Education and SES influence the risk for perinatal mortality and LBW. - Mothers from SSA had higher risk of LBW in Belgium. - Less LBW and preterm birth in individuals from Turkey, Maghreb and Eastern Europe in this study.	- Low SES is linked to a higher risk of LBW and therefore may be related to increased CKD and ESRD in individuals from low socioeconomic groups. - LBW may represent link between social and biological determinants of renal health

Preeclampsia (PE)	(Vikse et al., 2008) (5)	Population-based cohort study on the Norwegian population. - PE is associated with ESRD in the mother later in life. - RR differs according to numbers of gestations and numbers of episodes of PE: ≥ 1 gestation with PE during the first gestation has a ESRD RR of 4.7. ≥ 2 gestations and PE during the first gestation has an ESRD RR of 3.2, and PE in the second gestation RR 6.7. The highest ESRD risk is in women with many children and PE in 2-3 gestations with an RR of 15.5. - LBW in the offspring increased additionally the ESRD risk of the mother.	- The precise mechanisms of PE and later kidney diseases complex. - A possibility is the unmasking of underlying "silent" kidney diseases, or the damage of the kidney with subsequent proteinuria and possible reduced kidney function. - Additionally, PE and CKD have common risk factors (diabetes, hypertension and obesity).
	(Urquia et al., 2015) (92)	Register-based study on PE in immigrant women in Denmark, Sweden, Spain, Australia and Canada. - Compared to immigrants from Western Europe, immigrants from SSA, the Caribbean and Latin America, have the highest PE risk in this analysis (both OR 1.53). - Compared to the majority, all immigrants, except SSA had a lower OR for PE. SSA women had a higher OR for PE in Denmark (OR 1.2), Spain (OR 2.4) and Sweden (OR 1.2). - Compare to the majority, Caribbean/Latin American women had a higher OR for PE in Australia (OR 1.1), Canada (OR 1.2), Spain (1.8), not in Denmark or Sweden.	
	(Nilsen et al, 2018) (94)	Population-based cohort study on the Norwegian population. - PE is more rare in immigrants as compared to the general population. - Within the immigrant population, working immigrants had the lowest PE risk (O 0.5), and highest PE risk in refugees (OR 0.8).	- The risk for PE in immigrants may differ according to the reason for migration

	(Naimy et al., 2015) (93)	Population-based cohort study on the Norwegian population. - Generally, immigrants in Norway have less PE than the majority (OR 0.7):Lowest risk in immigrants from Vietnam (OR 0.4) or Afghanistan (OR 0.5), highest risk in immigrants from Somalia (OR 1.3, 1.1-1.4) and Philippines (OR 0.93, 0.8-1.1). - Duration of stay in Norway increases the risk for PE (< 5y OR 0.64, > 5y OR 0.91). After 5y, women from Somalia had a PE OR of 1.6 (1.3-1.9). No significant increase for women from Philippines	- Acculturation may increase the risk for PE
Socioeconomic status (SES)	(Patzer et al., 2012) (95)	Literature review on the link between SES and kidney disease. Low SES is linked to increased occurrence of CKD, faster progression, higher ESRD initiation rate and higher mortality.	The link between SES and diseases such as kidney diseases is complex and multidimensional (See also figure 4.2):
	(Morton et al., 2016) (38)	Literature review on patients with CKD 3-5 and patients on RRT. - Low income class and individuals not owning a house, ethnic minorities, low education and lack of health insurance was linked to increased cardiovascular mortality.	- Lower SES is e.g. linked with adverse behavioral and dietary habits, increased occurrence of obesity and diabetes, and also increased risk for adverse birth outcomes such as low birth weight.
	(Nicholas et al., 2015) (37)	Literature review with studies on CKD and ESRD in the US. - SES is strongly associated with incidence, prevalence and complications in CKD 3-5 and ESRD.	- Low SES is also linked to increased risk for cardiovascular mortality within patients with CKD.
	(Merkin et al., 2007) (96)	Cohort study in elderly Americans on SES and CKD progression. - Low neighbourhood affluence, low income and education was linked to increased progression of CKD, independently of diabetes or hypertension.	- Low SES is also interrelated with low education.
	(Bello, et al., 2006) (97)	Cross-sectional study on presentation of patients with CKD in UK. - Individuals from lowest SES present with lower GFR, as compared to individuals from higher SES. 2/3 of individuals from lowest SES presented at CKD 5, as compared to 20% in the most affluent group.	- Low SES is linked to later presentation to the nephrologist.

	(Vart et al., 2013) (99)	Cross-sectional study on the link between education or income with CKD in NL and US. - Netherlands: Strong association of low education with CKD prevalence. - US: Strong association of income with CKD.	- The health system in US is dependent on financial assets and insurance. - In NL, there is a universal health care coverage where the income plays a lesser role in access to health care services.
"Social deprivation"	(Caskey, 2013) (98)	Cross-sectional study. - Social deprivation is associated with increased incidence of RRT in UK. - Patients on RRT from socially deprived regions have a worse survival – <u>regardless of ethnicity</u>. - Whites from socially deprived areas have a more than 40% lower chance to receive an allograft compared to Whites from more affluent areas.	- The term "social deprivation" includes different variables such as income, SES, education, state of the neighbourhood, house ownership and so on. - In UK renal registry, "social deprivation" is not measured but identified by the postcode, that is linked to different "social deprivation variables" that are used as proxy. One of such an index is the "Townsend score".
Education and profession	(Adjei et al., 2017) (100)	Cross-sectional analysis of the HELIUS study. - In Dutch, low-level education and profession was linked to increased albuminuria, CKD 3-5 and high risk CKD according to the KDIGO 2012 classification - irrespective of origin - In Dutch and South Surinamese, low education and professional degree was consistently linked to higher odds for albuminuria, CKD 3-5 and high risk CKD. - All other groups (African Surinamese, Ghanaian, Turkish, Moroccan) had also a higher odds for the indicators - but insignificantly different after controlling for age/sex).	- Education is linked to SES and social deprivation. The relation of education to health state such as renal diseases is complex and multidimensional (see "Mechanisms" in "SES" above. Additionally, low degree education, linked to low degree profession is associated to more exposures to industrial nephrotoxins. - In most countries, ethnic groups attain lower degree of education and profession as compared to the majority.

Culture shaped habits, perceptions and attitudes	(Van Andel et al., 2010) (101)	Interview-based cross-sectional study on the use of traditional remedies in Surinamese in NL. - 75% of Surinamese in NL use traditional herbs - to promote their health, for prevention and to treat conditions. This was independent of age, sex, salary or educational attainment - 210 participants were in this study and 140 different herbal remedies were used. - Reasons for intake of such medicines where "habits", belief that it is more effective and has less adverse effects than school medicine.	- Culture can be defined as beliefs and customs that are shared by a group of people. - In many cultures, such as in SSA, it is a common custom to use herbal medicine as remedy, often prepared and prescribed by traditional healers. In Africa it is estimated that 80% of the population uses traditional herbal medicine, in China around 50% (140). - Such traditional medicines are not tested for safety. The kidneys (and liver), the main metabolizing organs, are in particular exposed for toxic damage.
	(Beune et al., 2008) (102)	Qualitative study on perception of hypertension treatment in Surinamese and Ghanaian in NL. - Ethnic groups tend to stop or reduce the dose of antihypertensive treatment and preferred alternative traditional treatment strategies. - Concerns were: Distrusting "chemical" compounds, becoming addicted, adverse reactions, sexual function, costs. - Trusting the physician positively influenced intake of antihypertensives	- Damage to the kidneys consist of acute tubular necrosis or tubulointerstitial nephritis and can be a consequence of 1) The own toxicity of the herb, 2) a mix-up of similar plants and administration of a toxic look-a-like plant, 3) contamination if this traditional medicine with heavy metals or industrial poison, or 4) interaction with other medication, e.g. suppression or induction of the metabolism of a drug by a nature medicine compound.
	(de Brito-Ashurst et al., 2010) (103)	Qualitative study on dietary habits in Bangladeshi in UK. - Participants mentioned that spices, including salt make food "strong", and thus eatable and "healthy". Unspiced/unsalted food was not digestible. - Traditional Bangladeshi food was not perceived as salty, but "strong". - Beliefs and culture-shaped preferences are important factors influencing increased salt-intake in Bangladeshi in UK.	- It is estimated, that at least 1/3 of all cases of acute kidney injury in Africa are caused by herbal medicine (123). - Culture also shapes the way how medical treatment is perceived and what kind of beliefs on e.g. possible adverse reactions people have.

	(Toselli et al., 2016) (104)	Literature review on how migrated Africans in Europe perceive body sizes. - Low SES and segregation was linked to an "ancestral" idea with large body sizes as the preferred shape in Africans living in Europe. - Higher SES and living in urban areas was linked to a more "modern" body size ideal with low weight being the preferred size. - The more "European", the more dissatisfied with body sizes.	- Culture influences the diet of patients and what patients perceive as "healthy food". - Culture influences perception of what is "healthy" and "beautiful". - In studies from SSA, e.g (131), a body shaped corresponding to overweight was seen as the most preferred body size, as it implied "wealth", "health" and "success". In contrary, being thin may imply diseases or low-degree profession with high physical activity, such as farming. - Renal transplantation from living kidney donors is an important resource as there are increasing numbers of patient on the waiting list for renal transplantation. - E.g. in UK, 35% of all renal transplantations are performed from living donors. - However, culture also shapes the attitude towards medical interventions such as kidney transplantation and may be a barrier for both living and deceased kidney donation.
	(Summers et al., 2014) (105)	Cohort study on kidney donation from deceased individuals in intensive care units in UK. - "Asian" ethnicity was associated to a 5-fold lower kidney donation rate as compared to White UK individuals. No data on patients with Black ethnicity.	
	(Rios et al., 2018)(106)	Questionnaire-based study on opinion on living kidney donations in Nigerian immigrants in Spain. - Less Nigerian immigrant as compared to Spanish or European immigrant had a positive attitude on living kidney donation: 30% of Nigerian immigrant had a positive, 70% had a negative attitude towards living kidney donation for related family members.	
	(Rios et al., 2018) (107)	Questionnaire-based study on opinion on living kidney donation in Uruguayan immigrants in Spain and the US. - All migrated Uruguayan living in Spain acknowledged donation of living donation of kidneys, compared to only 50% of those migrated to the US. - 2/3 of migrated Uruguayan in Spain were positive to donate kidneys after death as compared to 50% of those in the US.	

	(Bakewell et al., 2001) (108)	Questionnaire-based study on life quality in SA and White UK patients with ESRD. - Life quality was lower in SA than in Whites, irrespective of dialysis quality, in particular in PD. - Life quality in HD was similar, but Whites had more other health conditions - SA were more often socially deprived than Whites on dialysis. - Social deprivation was linked to worse mental and somatic health.	- Renal diseases, dialysis as well as undergone transplantation may represent a stigma for some populations. - PD may be more of a stigma in the case of SA, as this is performed home, and thus "closer to the family". PD may be culturally less compatible in this population.
Migration	(Agyemang et al., 2016) (110)	RODAM study. - In urban Ghana, the prevalence of obesity was 4-5-fold increased as compared to rural regions. Migrated Ghanaian men had a 15-fold increase and women a 6-fold as compared to rural non-migrated peers. - The prevalence of DM2 multiplied from rural to urban Ghana. Prevalence of DM2 in urban Ghana was similar to Europe. - Obesity was more common in London (> Amsterdam > Berlin). DM2 was most prevalent in Berlin (> Amsterdam > London).	- Complex interaction of migration with health: Health in migrants is influenced by different phases: 1) Pre-migration phase where health is influence by general socioeconomical and political conditions, as well as living conditions, health care services, social networks and, epidemiology and burden of disease of the home country), 2) Transition phase (Travel circumstances and conditions, duration, access to healthcare).
	(Agyemang et al., 2018) (111)	RODAM study. - High BP prevalence increases from rural to urban Ghanaian, and is 2-fold higher in migrated Ghanaian in Europe compared to rural Ghana. - Highest prevalence in Berlin (< Amsterdam < London). - Awareness of high BP is better in migrated Ghanaian. - Around half of all migrated Ghanaian with severe hypertension remained without treatment.	3) Arrival in host country with different socioeconomical and political, living conditions including acculturation aspects, health care services, social networks and epidemiology of diseases. - Upon arrival, immigrants gradually integrate and are exposed to a different environment and living circumstances. They may adopt e.g. a different lifestyle and dietary habits.

	(Brathwaite et al., 2017) (109)	RODAM study - Only a few people in Ghana smoke. - Upon migration to Amsterdam and Berlin, prevalence of smoking increases in women from 0% to around 3%, and nearly doubles in men - despite adjustment for education degree and profession. - Migrating Ghanaian to London, did not have an increase in smoking.	- Migration can have a <u>positive influence on health</u>, e.g. by increased security and improved living circumstances, like better occupation, food security, family reunification, better health system and so on.
	(Addo et al., 2017) (112)	RODAM study. - In urban Ghana and Europe: Increased SES and educational degree is linked to lower prevalence of diabetes. - In rural Ghana: Increased SES and educational degree is linked to higher prevalence of diabetes.	- Migration can have a <u>negative influence on health</u>, e.g. by exposure to another burden of disease, adoption of a different ("Western") lifestyle that can lead to obesity, social deprivation/shift in socioeconomic affluence, stress, mental diseases, integration issues such as language problems, isolation as well as mental diseases.
	(Sanou et al., 2014) (113)	Literature review on dietary habits of immigrants in Canada. - At arrival, immigrants are healthier than Canadian when it comes to NCD. This advantage deteriorates upon duration of stay. A reason for this deterioration is the "nutritional transition", a - Transition of dietary habits towards a "Western", caloric rich diet, that increases the risk for obesity, diabetes and hypertension. - Low SES is a reason for adoption of "unhealthy diet".	
	(Steffen et al., 2006) (114)	Literature review on the link between acculturation and BP. - Acculturation (measured as e.g. length of stay) is linked to increaseing BP, in particular when migration happened from rural to urbanized regions. - The increase in BP was unrelated to the body size - Mechanisms discussed are 1) Stress due to exposure to another culture and 2) change in physical activity and diet.	- <u>Length of stay</u>, a marker of acculturation, is often related to an adaptation of the immigrants living conditions to the host population, e.g. dietary habits

Access to healthcare	(Sarria-Santamera, 2016) (115)	Literature review on utilisation of health care services in immigrants. 28 articles on Europe. - Generally, immigrants use health care services less often than the host population. - Large heterogeneity of study populations and results. - Utilisation of health care services depended e.g. on origin, reason for migration and language skills. - Only one study with undocumented immigrants is referred.	- Migration is linked to how health care services are utilised. - UK, Netherlands, Denmark, Sweden, and Spain, where most studies are from, and also Norway, are countries where patients need to be referred to specialists by the primary health care services, like general practitioners.
	(Diaz et al., 2014) (116)	Register-based study on the usage of primary health care services by immigrants as compared to the majority in Norway. - Immigrants of ≥ 50 years from HIC attended less often to primary care han the majority. - Immigrants from LMIC aged 50-65 had more primary care contacts, but >65 years less contacts to primary care than the majority (OR 0.6). - Refugees had more, working migrants less contact primary health care providers. - Duration of residency was linked to increased use.	- Less utilisation of primary care may reflect a barrier, probably linked to factors like insufficient knowledge of the health care system or language issues -If there is less access to primary health care providers, then there may also be a barrier to access to specialist care, like to nephrologists. - Elderly immigrants and those who recently immigrated to Norway may therefore less chance to be referred to specialist care in case they have a kidney disease.
	(Cass et al., 2003) (117)	Register-based cross-sectional study from Australia. - Delayed referral of patients with advanced CKD to specialised care is linked to worse outcome, including higher mortality and less access to both transplantation list and transplantation in general.	- Timely referral to specialised nephrology care is important for the patient's outcome in CKD.
	(Udayaraj et al., 2010) (118)	Cohort study with patients on RRT in UK, assessing access to waiting lists for renal transplantation. - Individuals from low SES, and SA and Blacks had a lower chance of being listed. - After controlling, there was no difference in the chance of being listed between all groups. - In elderly patients, SA and Blacks had a higher chance of getting listed.	- In this study from UK, it was the SES, but not ethnicity, that was linked to the access to renal transplantation lists. - Reasons may be that low SES is linked to more diseases, and therefore less fitness for transplantation. Other factors may be problems with information and adherence, and travel expenses to be evaluated for transplantation in larger centres.

| Other aspects | (Hull et al., 2014) (119) | Cross-sectional survey on prescription of non-steroidal anti-inflammatory drugs (NSAIDs) of patients with CKD in UK.

- As CKD advances, patients are prescribed less NSAID.
- SA and Blacks are prescribed less NSAID than Whites.
- NSAID is thus not a reason for more ESRD In blacks in this study from UK. | - NSAID, analgetic and anti-inflammatory drug, is linked to CKD by different mechanisms, like by increasing BP and fluid retention, as well as tubulointerstitial nephritis.

- NSAID can be bought without prescription in many European countries, like also UK.

- There is no monitoring of (non-prescribed) NSAID use in CKD patient. |