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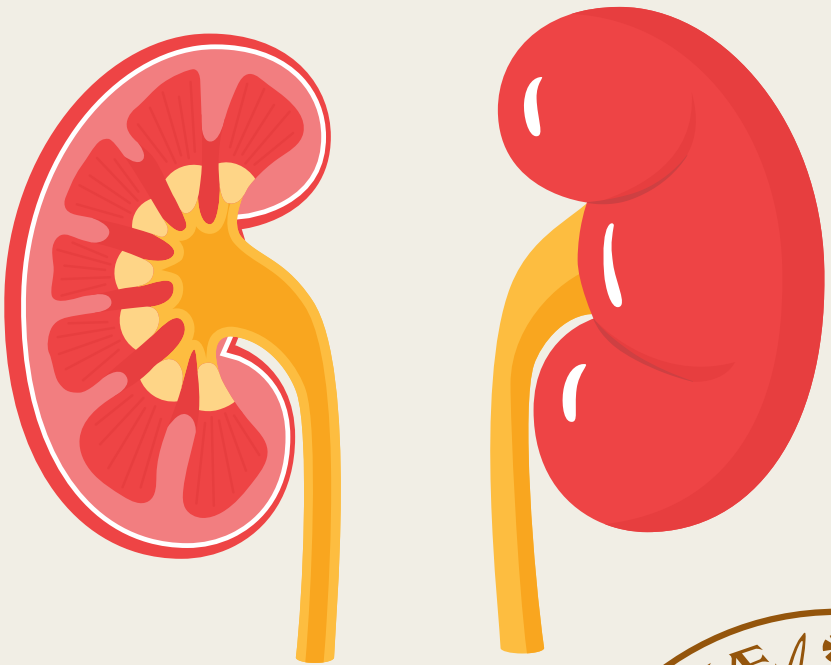

Aspects of ethnicity on blood pressure regulating mechanisms and kidney function in a defined population

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Title and subtitle: Aspects of ethnicity on blood pressure regulating mechanisms and kidney function in a defined population.

Abstract Background: Middle Eastern immigrants represent a growing population in Sweden today. This group are at higher risk for type 2 diabetes than the native population, but are also shown to exhibit unique properties; despite an abundance in traditional cardiometabolic risk factors such as obesity, dearranged blood lipids and diminished physical acitivity, this group seem to exhibit lower blood pressure levels. Further, people with type 2 diabetes of Middle Eastern descent have lower all cause and cardiovascular mortality rates, as compared to the native Swedish population. This indicates that Middle Eastern immmigrants may exhibit protective mechanisms towards cardiovascular diseases (CVD) that remain to be unravelled. Renal function is closely related to blood pressure. Further, new evidence on mechanisms in relation to blood pressure regulation and renal function has emerged, including vascular ageing, i.e. gradual change in the vascular structure and the endogenous opioid marker Pro-Enkephalin (PENK), which is shown to exhibit a direct cardiodepressive effect on the kidneys.

Aims: The general aim was to study potential differences across ethnicities on renal function, blood pressure and its regulating mechanisms as well as characteristics on diabetes and its complications - all of them, strongly associated with CVD. In specific, the aims were to study the contributing role of ethnicity (born in Iraq or Sweden) in each paper on: Renal function and its association with blood pressure (p*aper I),* diabetes traits and incidence in diabetic complications (p*aper II),* the biomarker PENK and its association with renal function (p*aper III) and a*rterial stiffness as an indicator of vascular ageing (p*aper IV)*. In this paper the aim was further to validate eGFR equations across a Middle Eastern ethnicity.

Methods: The thesis is based on data from three different cohorts comparing Iraqi and Swedish born subjects: the MEDIM study (p*aper I and III),* a population-based cross-sectional study, conducted in 2010-2012. The study included physical examinations, blood sampling and collection of information on lifestyle, comorbidity and medication. The ANDIS study (*paper II),* a longitudinal follow-up study, recruiting patients diagnosed with diabetes during 2008-2016 and followed for complications until 2017. The MEDIM 2019 population-based study (*paper IV),* a cross-sectional study conducted in 2019-2020 assessing iohexol clearance for determining measured GFR (mGFR), pulse wave velocity (PWV) as measurement of arterial stiffness, physical examinations, blood sampling and information on comorbidity, lifestyle and medication.

Results: In *paper I,* Iraqi-born immigrants (n=1214) exhibited a better renal function as described by higher levels of estimated GFR (eGFR) in comparison to the Swedish-born control group (n=659) (96.5 vs 93.6 mL/min/1.73m^2, p=0.009). Further, the association between blood pressure and renal function was significantly weaker in the Iraqi group as confirmed by a signification interaction ($P_{\text{interactinon = Country of birth x eGFRCAPA}}$=0.004). In p*aper II,* a larger proportion of Iraqi-born immigrants (n=183) had insulin-deficient diabetes in comparison to the Swedish-born control group (n=7044) (27.9 vs. 16.2%, p<0.001) and a lower proportion had insulin-resistant diabetes (5.5 vs. 16.3%, p<0.001). The risk for chronic kidney disease (CKD) among diabetes patients was lower in the Iraqi-born group (HR 0.26, 95% CI 0.08-0.8). In p*aper III,* levels of PENK did not differ between Iraqi-born immigrants (n=1263) and the Swedish-born control group (n=680), despite higher eGFR in the Iraqi group. The association between PENK and renal function was weaker in the Iraqi group as supported by a significant interaction ($P_{\text{interactinon = Country of birth x PENK}}$=0.031). In *paper IV,* PWV did not differ between Iraqi-born immigrants (n=31) and the Swedish-born control group (n=32). When comparing mGFR to eGFR based on various equations, the commonly used CAPA equation was less accurate in the Iraqi group. The results indicated that the CKD-EPI equations could be accurate equations in the Iraqi group.

Conclusion: Iraqi born immigrants had a more favorable renal function, an insulin deficient diabetes trait and considerably lower risk for diabetic kidney disease, than for the native Swedish population. The impact on renal function of blood pressure as well as of the cardiodepressive opioid PENK was weaker among Iraqi-born immigrants, which may contribute to a preserved renal function in the Iraqi-born group. In the long run, a more favorable renal function and less susceptible kidneys could serve as an important advantageous mechanism in the protection against CVD among Iraqi-born immigrants.

Key words: Arterial stiffness, Biomarkers, Blood pressure, CVD, eGFR, Ethnicity, Migration, Pro-Enkephalin, Renal function

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Contents

List of Papers

The papers included in this thesis are listed below. They are referred to their Roman numerals in the text.

I. **Nilsson C**, Christensson A, Nilsson PM, Bennet L. Renal function and its association with blood pressure in Middle Eastern immigrants and native Swedes. Journal of Hypertension. 2017; 35(12):2493-2500

II. Bennet L, **Nilsson C**, Mansour-Aly D, Christensson A, Groop L & Ahlqvist E. Adult-onset diabetes in Middle Eastern immigrants to Sweden: Novel subgroups and diabetic complications—The All New Diabetes in Scania cohort diabetic complications and ethnicity. Diabetes/Metabolism Research and Reviews, 2021;37(6):e3419

III. **Nilsson C**, Christensson A, Nilsson PM, Melander O, Bennet L. Pro-Enkephalin and its association with renal function in Middle Eastern immigrants and native Swedes. Scand J Clin Lab Invest. 2021; 28:1-6

IV. **Nilsson C**, Christensson A, Nilsson PM, Bennet L. The accuracy of eGFR estimation and arterial stiffness in a Middle Eastern population residing in Sweden – A cross-sectional study. (Manuscript)

List of Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensinogen Converting Enzyme
ACR	Albumin/Creatinine Ratio
ADH	Anti Diuretic Hormone
AKI	Acute Kidney Injury
ANDIS	All New Diabetics In Scania
APOL1	Apolipoprotein L1
AUC	Area Under the Curve
BMI	Body Mass Index
CAPA	Caucasian, Asian, Pediatric and Adult
CG	Cockcroft and Gault
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
DASH	Dietary Approaches to Stop Hypertension
DKD	Diabetic Kidney Disease
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
EVA	Early Vascular Ageing
FRS	Framingham Risk Score
GADA	Glutamic Acid Decarboxylase Antibody
GBD	Global Burden of Disease
GFR	Glomerular Filtration Rate
GRS	Genetic Risk Score
GWAS	Genome-Wide Association Studies
ISI	Insulin Sensitivity Index
ISR	Insulin Secretion Rate

KDIGO	Kidney Disease Improving Global Outcome
KIM-1	Kidney Injury Molecule-1
LMrev	Revised Lund-Malmö
MARD	Mild Age Related Diabetes
MDRD	Modification of Diet in Renal Disease
MEDIM	impact of Migration and Ethnicity on Diabetes In Malmö
MENA	Middle East and North Africa
mGFR	Measured Glomerular Filtration Rate
MOD	Mild Obesity related Diabetes
NGAL	Neutrophil Gelatinase-Associated Lipocalin
PENK	Pro-Enkephalin A
PP	Pulse Pressure
PWV	Pulse Wave Velocity
RAAS	Renin Angiotensin Aldosterone System
SAID	Severe Autoimmune Diabetes
SPS	Shrunken Poor Syndrome
SBP	Systolic Blood Pressure
SIDD	Severe Insulin Deficient Diabetes
SIRD	Severe Insulin Resistant Diabetes
SNP	Single Nucleotide Polymorphism
TIMP-2	Tissue Inhibitor of Metallo-Proteinases 2
WHO	World Health Organization

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Introduction

Migration and health

We reside in a world being globalised at an increased pace. Due to wars, conflicts and government persecution, many people have been forced to flee their native countries during the last decades. By the end of 2020, 19.7% of the Swedish population were born abroad, in comparison to 11.3% in 2000 (1). Between these two decades, an increasing number of people have fled from the Middle Eastern region - from Iraq and Syria in particular. The changing demography affects the panorama of diseases and the need for research on the matter is evident, in the long run to ensure equal healthcare.

Migration and health are today recognised as a global health priority (2) – the following thesis is an acknowledgement to this.

Middle Eastern Immigrants and health

The Middle East

The definition of the Middle East is somewhat an unstable construction and there is a lack of consensus on the definition and when to use it. Many global organisations use the construct MENA (Middle East and North Africa) further demonstrating the indefinite way to use the Middle East definition. Countries often included in the Middle East are heterogeneous in development levels, ranging from among the world's richest countries including Qatar and the United Arab Emirates to one of the world's poorest countries, Yemen.

It has for long been known that the Middle Eastern region exhibits disproportionately high rates of type 2 diabetes (3). Thus, most research initiatives on Middle Eastern immigrants living in Western countries, have primarily focused on diabetes and reported increased prevalence rates of the disease among this group (4, 5). Research on other cardiovascular risk factors is more lacking and the research is heterogeneous in general.

Many of the studies focusing on Middle Eastern immigrants examine populations from a mix of countries, or with no specifications on the composition. A thorough review going through existing research on Arab Americans and their health

concluded that nearly 50% of the existing studies, within the field, did not specify the study populations included thus making comparisons challenging (6).

Previous studies on blood pressure in specific include the Norwegian 'The Oslo Immigrant Health study' that was conducted in 2002, based on first-generation immigrants from Iran, showing lower prevalence of hypertension in this group in comparison to immigrants from Turkey, Pakistan or Sri Lanka. No comparison was made against a native control population (7). A 2019 population-based Spanish study from Catalonia, which used a local healthcare database, disclosed lower rates of hypertension among immigrants from North Africa/Middle East, than in the native population (5). A Canadian retrospective study also showed lower rates of hypertension among Middle Eastern immigrants, than in a non-immigrant population, thus higher rates of diabetes (8). A smaller (n=80) Danish study including male native Danes and Afghanistan-born immigrants, investigated 24-hour ambulatory blood pressure monitoring (ABPM) and salt sensitivity, and showed the Afghani group with lower ABPM and less sensitivity to a change in salt intake (9). A US study based on a National Health Interview Survey, including almost 42,000 immigrants from various areas, showed higher rates of diabetes but not hypertension in the Middle Eastern group (4).

Similar studies on renal function are sparse. A Swedish cohort study based on the National Patient Register showed that immigrants born in Iraq had an increased incidence of end-stage renal disease (ESRD), both for women and men. However, individuals born in Iran did not show this trait. The increased risk disappeared among second-generation immigrants (10). On the contrary, a Canadian Ontario-based population study using administrative health datasets reported that the rate of ESRD requiring dialysis was lower among immigrants from the Middle East, in comparison to long-term Canadian residents (11).

Recently, a Swedish register study based on the national "Swedish Prescribed Drug Register" showed lower rates of cardiovascular mortality as well as all-cause mortality among immigrants from the Middle East with diabetes, in comparison to native Swedes. In general but without extrapolated data for Middle Eastern immigrants, the lower risk disappeared among second-generation immigrants (12). The Canadian Ontario-based population study showed similar results (11).

Subsequently, there is a gap of knowledge on contributing risk factors to cardiovascular diseases (CVD) within this population. Previous studies often lack comparisons with the native population, and very few studies have been designed to examine cardiovascular risk factors specifically in this group.

The MEDIM study

A Swedish research initiative on Middle Eastern immigrants is the MEDIM (impact of Migration and Ethnicity on Diabetes In Malmö) study that was designed and conducted in Malmö, Sweden during 2010-2012, with the aim to further investigate and aid in the understanding of mechanisms behind the increased risk for type 2 diabetes in Middle Eastern immigrants.

At this time, the largest group from the Middle East residing in Sweden was Iraqi-born immigrants, thus this group were chosen as a representative for the Middle Eastern immigrant population in general. Iraq has been in excessive turmoil during the last decades with wars and has been at the centre of the ISIL invasion during the 2010s, which forced millions of people to flee their land. The population is of Arabic origin - to a large extent - but Iraq is also known as an ethnically diverse country including Kurds and Turkmens.

Figure 1. A map of Iraq (green in the middle) and its neighbouring countries. Copyright iStock by Getty Images.

The MEDIM study compared Iraqi-born immigrants in Sweden with a control population born in Sweden recruiting over 2000 participants and included metabolic profiling as well as data on socioeconomic factors and lifestyle (13). MEDIM concluded that prevalence of type 2 diabetes was around twice as high in the Iraqi group (11.6% vs. 5.8%) (14). Being born in Iraq was a risk factor for developing diabetes, independent from other traditional risk factors. Further, within the Iraqi

group, there was a cluster of cardiometabolic risk factors including physical inactivity, obesity, abdominal obesity and hypertriglyceridaemia (14). CVD risk has also been studied in the original MEDIM population showing higher self-reported prevalence of CVD in the Iraqi population, if diagnosed with diabetes type 2, but lower prevalence if diabetes-free (13).

Contradictory, despite the profusion of traditional risk factors, mean blood pressure levels were paradoxically lower in the Iraqi born group (15).

Considering the lower all cause and cardiovascular mortality rates among Middle Eastern immigrants, this might suggest that this group exhibit protective properties against CVD involving a more favourable blood pressure regulation, thus - the main theme of this thesis was born.

The contributing role of ethnicity to diseases

The matter of using race/ethnicity within medicine is debated, especially during recent years, in line with the ongoing debate in society. Our history contains a profound number of examples of injustice and its argued that the use of race and ethnicity within medicine sustains inequality (16). In 2020, the 'American Medical Association' adopted a new policy to recognise race as a social construct, rather than a biological construct (17), which has been further argued in high impact journals, proposing that the use of race should be reconsidered (18). The debate also contains voices arguing that it would be inappropriate to fully abandon race and ethnicity in clinical practice and research, as these variables are able to capture important epidemiological information and in turn could contribute to explain racial and ethnic health inequalities (19).

By that means, differences in health and health outcomes between ethnic groups are well known and studied. An apparent example is single gene disorders, such as cystic fibrosis being highly prevalent in northern Europe (20) and thalassemia in the Mediterranean region (21). More complex diseases including type 2 diabetes or hypertension, which are not solely genetic diseases, are also affected by genetic factors as well as by epigenetics i.e. the modifying role of behaviour and environment on the expression of genes and gene activity, which partly explains the increased risk of cardiometabolic diseases in certain populations (22). Environmental factors including lifestyle, cultural norms and a poor socioeconomic situation, play a considerable role in the contribution to these conditions (23-25). Socioeconomic disparities are common between ethnic groups (26) and a worse socioeconomic situation is a strong predictor for poor health outcome, exemplified in Sweden with refugees living in more socioeconomically vulnerable areas being at increased risk for developing diabetes than their counterparts residing in less vulnerable areas (27).

Migration and health – a bidirectional relationship

The relationship between migration itself and health outcome could be viewed from different angles. In general, the migration process requires strong physical and mental abilities. This might render a selection of individuals with better health than for the general population, endorsing a 'healthy migrant effect' (28). Previous studies have shown that immigrants experience better health in comparison to native inhabitants during the first years in their new country (16, 17). Further, a US study concluded that immigrants in general, lived 3.4 years longer than the population born in the US (29).

In contrast, migrants are regularly viewed as a vulnerable group, that in general, exhibit worse health outcomes (30).

Factors affecting health outcomes among migrants include both pre-migratory and post-migratory ones. Pre-migratory factors include *social factors* in the country of origin (such as income and access to health care) and *environmental factors* (weather, toxins, exposure to war and political repercussions) (31). In the post-migratory phase, factors like economic insecurity, the social situation including access to health care, possible discrimination and lifestyle changes play a considerable role (32, 33).

Of interest, over time, - health factors among migrants tend to resemble the host population, a phenomenon often explained by changes in lifestyle and socioeconomic factors (34, 35).

Renal function

Blood pressure is strongly related to the kidneys, both regulatory and pathophysiological, which will be outlined below. With the paradoxical low blood pressure in the Iraqi group, renal function within this group emerged as a fundamental topic to study further.

The kidneys and their function

The human kidneys carry out a variety of important tasks within the body, which includes excretion of waste products, regulating acid-base balance, fluid balance, electrolyte concentrations and blood pressure. The kidneys also stimulate the production of red blood cells through erythropoietin and convert 25-(OH) vitamin D into active D vitamin (1,25 dihydroxy-vitamin D) for calcium homeostasis (36-39).

The kidneys are located retroperitoneally alongside the spine measuring around 10-13 cm each. Blood from the systemic circulation reaches the kidneys through the renal arteries with the amount of approximately 1-1.25 L/min rendering 20-25% of the total cardiac output (blood flow the heart) directed to the kidneys (40).

The kidneys functional unit is the nephron, which contains a capillary network called a glomerulus, Bowman's capsule and a renal tubule. Each kidney consists of around one million nephrons (41).

Kidney diseases are broadly divided into acute kidney injury (AKI) and chronic kidney disease (CKD), with this thesis focusing on the latter.

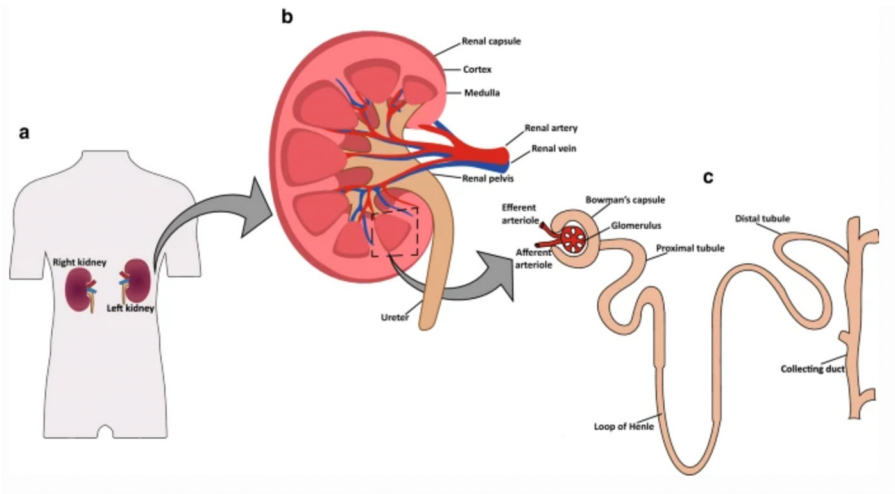

Figure 2. The human kidneys. a. external view b. internal view c. nephron. Faria J, *et al*. Arch. Toxicol (42). With permission from SpringerLink.

Chronic kidney disease

According to the 'Kidney Disease Improving Global Outcomes' (KDIGO) guidelines from 2012, CKD is defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 during at least three months (43). CKD could be further categorised into different stages (Table 1) (44).

Table 1. Stages of CKD.

eGFR (mL/min/1.73m^2)	CKD stage	Renal function
≥90	G1	Normal or high
60-89	G2	Mildly decreased
45-59	G3a	Mildly to moderately decresead
30-44	G3b	Moderately to severely decreased
15-29	G4	Severely decreased
<15	G5	Kidney failure

The two major causes of CKD in the developed world are diabetes and hypertension (45). In developing countries, aetiologies are more heterogeneous - with for instance HIV and environmental toxins causing a large proportion of cases such as pesticides and herbals (46). It should, however, be pointed out that CKD caused by hypertension is criticised as a concept, considering that most CKD patients develop hypertension during the disease course itself. Hypertensive changes in a kidney biopsy are non-specific and could rather reflect a late diagnosis or insufficient diagnostics (47). As of today, we surely lack knowledge on the spectra of different kidney diseases, especially the ones that run in families.

Previous reports from the US have described that as much as approximately 30% of patients with type 1 diabetes and 40% of patients with type 2 diabetes develop signs of diabetic kidney disease (DKD) (48, 49). The development of DKD is associated with several structural changes in the kidneys. Classically, the characteristics include thickening of the glomerular basement membrane, mesangial volume expansion, nodular glomerular sclerosis and tubulointerstitial fibrosis (50, 51). Clinically the pattern has been described as primarily glomerular hyperfiltration (higher GFR) progressing to albuminuria with subsequent decline in GFR (52). However, studies during the last decade have shown that the disease presents itself in various ways, not always following the classic pattern. For instance, a 2016 autopsy study for instance, indicated that DKD may be underdiagnosed with several objects not exhibiting classical hallmarks such as albuminuria or lower GFR (53).

The prevalence of CKD globally was in 2017 estimated to be around 9.1% by the Global Burden of Disease (GBD) study (54). Another meta-analysis using a different collection of data has estimated an even higher rate of 13.4% thereby enlightening the uncertainties surrounding these numbers (55). The GBD study further estimated that 1.2 million deaths in 2017 were attributed to CKD (54).

It is well known that reduced renal capacity is closely associated with increased risk of death and CVD – CKD patients are actually more likely to develop CVD, than to develop more severe stages of kidney failure and reach ESRD (56).

The risk for CVD is potentiated by diminishing renal function, with the risk rising sharply for subjects with an eGFR below 45 mL/min/1.73m^2 (57). The mechanisms

behind the CVD risk can be viewed from different angles. Firstly, there is an abundance of traditional risk factors among CKD patients including hypertension, diabetes and dyslipidaemia among others (58). Traditional risk factors, however, cannot solely explain the CVD risk as illustrated by the general inaccuracy for the Framingham Risk Score (FRS) prediction algorithm among CKD patients (59). The additional risk augmentation is thought to depend on different mechanisms. For instance, with reduced function, the kidneys release hormones, enzymes and cytokines at increased pace that can lead to vasculature changes, atherosclerosis and specific media calcification of elastic arteries (60, 61). In addition, accumulation of uremic toxins and hemodynamic alterations, such as volume overload, strongly increases the CVD risk (62, 63). Other risk factors for CVD, which may be amplified among CKD patients include anaemia and malnutrition (64).

Chronic kidney disease and ethnicity

There are known disproportions in CKD prevalence between different populations; Some of the increased risk for CKD in certain populations can be attributed to differences in the burden of traditional risk factors, but research has shown that the increased risk persists also when adjusting for those factors. (65). The vast majority of studies on CKD and its progression, which focus on ethnicity, have been concentrated on African Americans in the US. It is well known that African Americans exhibit higher risk for CKD progression in comparison to Caucasians. Much attention has been given to variants in the Apolipoprotein L1 (*APOL1*) gene, as African Americans present with high prevalence rates of its high-risk alleles, contributing to increased CKD risk within this group. APOL1 increases the risk of several types of kidney diseases including hypertension associated ESRD, focal segmental glomerulosclerosis and HIV associated nephropathy. The relationship between *APOL1* and DKD is more unclear as studies have not been able to show that *APOL1* increases prevalence in DKD but may increase the progression rate (66).

Another example of populations exposed to certain CKD traits is the ‘Mesoamerican nephropathy’, mainly affecting male agricultural workers in the Central American pacific west coast, with high rates of CKD and ESRD, with no correlation to traditional risk factors (67). Another famous example is the ‘Balkan endemic nephropathy’ with signs of chronic tubulointerstitial nephritis among residents of farming villages along the Danube River in Balkan, which is thought to be caused by aristolochic acids (68, 69).

Knowledge on prevalence rates of CKD in Middle Eastern populations is lacking. The GBD study presented an age-standardised prevalence rate of CKD of 10.9% in Iraq in comparison to 6.8% in Sweden, however, based on insecure data (54). A meta-analysis from Iran found 18 relevant studies on prevalence rates for ESRD, with rates varying between 55 to 818 per million people (70) also highlighting the lack of reliable epidemiological data in this area.

Assessment of renal function

The important task of assessing renal function is a comprehensive topic and still heavily researched. Today's precision medicine makes proper assessments fundamental.

The most widely used marker of renal function is GFR. Each nephron filters a certain amount and GFR is basically the average filtration rate from each nephron multiplied by the total number of nephrons (71). There is an individual variation in GFR, depending on factors such as age, sex, size, etc. It is also affected by food intake and activities; hence it varies during the day (72-75). As the individuals differs in size, GFR is indexed for the body surface area and expressed as per $1.73m^2$ to enable comparisons between individuals (76).

Since GFR cannot be measured directly in clinical practice, we routinely assess GFR from either clearance measurements or from levels of indirect filtration markers in the blood. Ideally, measured GFR (mGFR) should be used, based on clearance methods. The golden standard method has long been inulin clearance, which classically includes constant intravenous infusion and timed urinary samples (77), however, this is a time consuming and complex assessment which has rendered the development of other robust clearance methods including iohexol clearance.

Iohexol clearance uses the non-ionic contrast medium iohexol first described for human use in 1980 (78). It is believed to be freely filtered through the glomerulus as it exhibits low molecular weight and low protein-binding properties (79, 80). Also, the extra-renal clearance is limited (between 2 to 3 $mL/min/1.73m^2$) (81, 82) thus making it a suitable GFR marker. Iohexol is injected as a bolus dose for subsequent urinary, or most commonly plasma sampling of iohexol concentration for clearance measurement. After injection of iohexol, the concentration depends on the distribution between the intra- and extravascular volumes (fast phase) and later the elimination (clearance) by the kidneys (slow phase) (80, 83). It is ideal to measure iohexol concentrations in both phases for calculating the area under the curve (AUC), although, with the necessity of concentration samplings very frequently in the beginning. To facilitate an easier process, correction models have been developed to calculate AUC during the slow phase and correct for the fast phase (84). The choice of timing and number of samples is cumbersome and depending on what GFR levels to expect (85, 86), i.e. with normal GFR, the last sampling could be done four hours after iohexol injection but in cases with severely decreased GFR, the last sampling needs to be performed 24 hours post injection. Commonly used in clinical practice, it is the one-sampling method with obvious practical advantages (87), which has shown good accuracy (88).

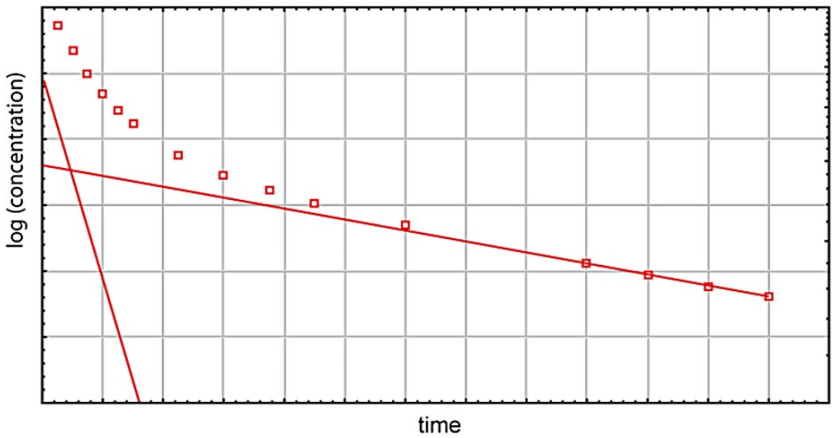

Figure 3. Elimination of iohexol from plasma after a single injection representing the fast and slow phase. Delanaye P, *et al*. Clin. Kidney. J. 2016 (89). With permission from Oxford University Press.

As clearance methods are regarded as costly and somewhat cumbersome in daily practice, GFR is usually estimated from endogenous biomarkers - most commonly creatinine or cystatin C (90, 91).

Creatinine is generated from the breakdown of creatine phosphate in muscles and the elimination process consists of filtration by the glomerulus (92) but also secretion in the proximal tubule (93). Generation of creatinine is affected by diet and muscle mass rendering variations in plasma levels dependent on age, sex and ethnicity (94, 95).

Cystatin C is a proteinase inhibitor that is produced by all nucleated cells in the body at a constant rate (96). It is freely filtered through the glomerular membrane and thereafter reabsorbed and metabolised in the proximal tubule (97). In comparison to creatinine, cystatin C has been shown to work independently from age, gender, height and muscle mass (98). However, other influencing factors are more uncertain. For example, it is suggested that high doses of corticosteroids, obesity and inflammation may affect the production of cystatin C (99-101).

There are numerous equations for calculating eGFR from either creatinine and/or cystatin C. The first widely recognised equation was published by Cockcroft and Gault in 1973, based on age, weight, height, creatinine and correction factors, mostly derived from hospitalised men with pre-existing CKD, i.e. 'CG-equation' (102). Another widely used formula was derived from the 'Modification of Diet in Renal Disease' study, subsequently named the MDRD equation (103), also furthermost based on a population with pre-existing CKD. The CG-equation is regarded to overestimate the true GFR while the MDRD-equation rather underestimates it, especially on subjects with normal renal function (104).

Hence, efforts have been done to find new more accurate equations. In 2009 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was introduced (105) outperforming the previous equations (106), especially in situations with higher eGFR, and is therefore the recommended choice in the KDIGO 2012 guidelines (107). CKD-EPI utilises both a creatinine-dependent, cystatin C-dependent as well as a combined equation.

Scandinavia has a long tradition in research on GFR assessment. In particular - two eGFR equations has been developed, the revised Lund-Malmö (LMrev) equation, based on creatinine, and the "Caucasian, Asian, Paediatric and Adult" (CAPA) equation, based on cystatin C (108, 109). LMrev is developed in a Swedish born population and has been shown to be more accurate in comparison to the CKD-EPI and MDRD equations in that population (108). The CAPA equation is derived from a population including Swedish and Japanese adults as well as Swedish and Dutch children (109). As of today, LMrev and CAPA are the main employed equations in routine practice in many parts of Sweden but lack full global recognition.

The process of assessing the credibility for an eGFR-equation consists of a comparison between eGFR and mGFR based on an acknowledged method. The comparison typically uses three metrics; (110).

- *Accuracy* describes the proportion of eGFR values within mGFR of a certain percentage (often ±30%).
- *Bias* describes the mean/median difference between eGFR and mGFR.
- *Precision* describes the variability of differences which could be described as standard deviations or interquartile ranges (IQR).

Ethnicity and eGFR.

In 1997 it was described that creatinine excretion was strongly affected by ethnicity, when comparing African Americans versus non-African Americans in the US, which led to underestimation of creatinine clearance (CG) among African Americans (111). Subsequently, both MDRD and CKD-EPI have added a 2-level variable for race/ethnicity (usually described as black vs. non-black). The matter has been further studied among residents in the US. It is, however, believed that there are existing differences in other ethnical groups as indicated by improved performance of the MDRD equation in both China and Japan, after the introduction of a Chinese and Japanese coefficient (112, 113).

There is widespread criticism on the use of race-based adjusting variables in GFR estimation. In 2020, a task force was established by the 'US National Kidney Foundation' and the 'American Society of Nephrology' to reassess whether race variables should be included in GFR estimation, or not. The conclusion was

published in September 2021, calling for the removal of the race variable. The rationale included that all estimations have limitations, and that bias and inaccuracy should not be concentrated within one specific group. Hence, following the acknowledgment of estimating limitations, the task force also called for national efforts to facilitate an increased use of cystatin C (114).

There is limited research on the accuracy of GFR estimation in populations of Middle Eastern descent. A Saudi Arabian study from 2008 investigated mGFR based on 51CrEDTA among 90 potential kidney donors and compared mGFR with eGFR based on the CG- and MDRD equations, reaching the conclusion that the CG equation was superior. The authors also proposed a correction factor to the equation (115). Another Saudi Arabian study with a smaller study population (32 participants) and more deteriorated renal function, on overall showed better correlation with the MDRD- vs. CG equation in comparison to inulin clearance (116), further enlightening the heterogeneity of the matter. A more recent Saudi study from 2016 declared CKD-EPI based on creatinine alone as superior to CKD-EPI based on Cystatin C alone or in combination with creatinine, as well as to the MDRD equation when compared to inulin clearance (117).

Altogether, most of the studies including a Middle Eastern population have been performed in the well-developed Saudi Arabia and have, so far, been too limited for validation purposes.

Albuminuria

Albuminuria is another widely used marker for renal function. Albumin is a serum protein synthetised in the liver, with an integral role in maintaining oncotic pressure for body fluid distribution. It also functions as a transport protein. The molecular mass of albumin is approximately 66 kiloDalton (118). Under normal circumstances, the kidneys do not filter large molecules into the urine. Glomerular diseases such as diabetes nephropathy can affect the permeability of the glomerular capillary wall, rendering increased permeability leading to urinary passage of proteins such as albumin to the tubule. The reabsorption in the tubule could also be affected. Altogether this leads to increased leakage of albumin into the urine (119). Albuminuria can be detected, but not properly quantified by urine dipsticks. For quantification, albumin could be measured from a 24-hour urine collection, but this procedure is of course cumbersome in routine practice. Commonly the concentration is therefore measured in a spot sample, expressed in the unit mg/L. Since the urine concentration varies, the amount of albumin is compared to the concentration of creatinine, giving the measurement albumin/creatinine ratio (ACR) with the unit g/mol (120). From urinary ACR, albuminuria can broadly be categorised into three categories.

Table 2. Albuminuria categories.

uACR (g/mol)	Category	Category
<3	A1	Normal to midly increased
3-30	A2	Moderately increased
>30	A3	Severely increased.

If urinary ACR is above 220 g/mol accompanied with low serum albumin, its regarded as nephrotic syndrome, which is potentially life-threatening with increased risk for thromboembolism and infections.

In clinical practice, nephrologists usually investigate other proteins in the urine including low molecular weight proteins such as protein HC and Immunoglobulin G (IgG), which may reflect tubulointerstitial diseases if elevated (121).

Proposed biomarkers

The "Biomarkers Definitions Working Group" defines a biomarker as *"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (122).* The most important characteristics for a useful biomarker are accuracy, reproducibility and easiness to measure. As the entire spectrum of a disease could be reflected by biomarkers, they could aid in prediction, diagnosis as well as in understanding the cause (mechanisms) of diseases.

Considering the previously mentioned limitations for creatinine and cystatin C, the medical and research community have long searched for new biomarkers of renal function (123). Most research focus has been directed to settings of acute kidney injury, as the traditional markers are especially limited during acute changes and may delay diagnostics of AKI (124). In 2020, an expert group presented a consensus statement at the 'Acute Disease Quality Initiative meeting', elucidating the need for further research but also suggesting that biomarkers should be used to identify high-risk patients, improve diagnostic accuracy of AKI, improve processes of care as well as assist in the management of AKI. The suggested biomarkers include Kidney injury molecule-1 (KIM-1), tissue inhibitor of metallo-proteinases 2 (TIMP-2), neutrophil gelatinase-associated lipocalin (NGAL) and Pro-Enkephalin A (PENK) among others (125).

The process for a new biomarker to reach wide acceptance is far from easy, perhaps best illustrated by cystatin C, which has been used in Swedish clinical laboratories in daily practice for decades, but is yet to be a conventional analyse in the US (126). Thus, most of the biomarkers listed above will most likely never become tools for daily clinical use.

Pro-Enkephalin (PENK)

A new biomarker of particular interest is PENK. As early as 1975, the first endogenous opioids were discovered, which were named enkephalins (127). The enkephalins include subgroups that are biologically active (i.e. met-enkephalin, leu-enkephalin), acting mostly on delta opioid receptors (128). Enkephalins are known to play a role in the modulation of pain and behaviour, among others and subsequently found in great numbers in the central nervous system (129). In animal research, the precursor PENK was also abundant in non-neural tissues such as the kidneys (130), making it intriguing to study from a renal perspective as well. The biosynthesis of enkephalins uses several steps, one of which is the cleavage of the precursor protein PENK, which has been shown to be stable enough for direct analysis in plasma hence working as a surrogate marker for enkephalins (131).

As of today, PENK is predominantly studied as a biomarker for renal function, as high levels of PENK in plasma are associated with lower eGFR levels (132). As for most biomarkers, the research has mostly focused on acute clinical settings, including myocardial infarction and sepsis populations (133-135), but PENK does also correlate well with mGFR in stable and healthy subjects (136). Further, PENK has been shown to predict future decline in renal function as higher baseline PENK predicted significantly greater annual decline in eGFR during a mean follow-up time of 16.6 years (137). The same study also established a casual genetic relationship between PENK and CKD.

The exact function of enkephalins in the kidneys are currently not fully understood, but it has been shown that they induce beneficial cardiovascular effects through the opioid effect – reducing the heart contractility, hence lowering blood pressure and heart rate. Enkephalins are also suggested to induce diuresis and natriuresis (138, 139).

Blood pressure and arterial stiffness

Blood pressure regulation

The term ‘blood pressure’ is referring to the pressure within large arteries in the systemic circulation, i.e. arterial pressure. *Systolic* pressure is defined as the maximum pressure when the heart is contracting, and on the contrary, *diastolic* pressure is defined as the pressure during the heart relaxation between beats. The pressure (mmHg) correlates to cardiac output, arterial elasticity and peripheral vascular resistance. The regulation consists of several different mechanisms but is still not completely understood. However, the kidneys play a crucial role (140) by the *renin-angiotensin-aldosterone system* (RAAS) affecting the blood pressure

regulation through vasoconstriction, sodium and water reabsorption among others (141, 142).

Hypertension

Hypertension is defined as persistently elevated blood pressure; the exact definition varies somewhat. US guidelines emphasises a threshold of 130/80 mmHg for mild hypertension (143) while European guidelines uses the threshold 140/90 mmHg (144). Classically, hypertension is divided into essential and secondary hypertension, the latter including aetiologies such as Cushing's syndrome and renal artery stenosis, which however is not the scope of this thesis (145). The vast majority of hypertension cases are classified as essential hypertension. Prevalence rates of hypertension are high and age-dependent, possibly around 30-45% in Europe (146).

Genetics and environmental factors (147) play a complex role in the development of hypertension. The exact aetiology, however, remains to be unravelled. Strong risk factors include increasing age, sedentary lifestyle, smoking, low socioeconomic status and increased salt intake in salt-sensitive subjects among others (148-150).

Salt intake is of interest as it interferes with the natural blood pressure regulating mechanism by means that are not fully understood, although is believed to involve modifying the RAAS activity, activation of the sympathetic nervous system and increased peripheral resistance (151-153). The effect of salt intake on blood pressure is well studied in large multi-centre studies (154) but could be further illustrated by the Yanomamo Indians, an indigenous tribe in the rain forest of Brazil and Venezuela that use a diet with no salt. In 1975, it was shown that blood pressure in this group did not increase with ageing. Blood sampling also showed high renin and aldosterone activity acting as a proxy of the likely characteristics for humans before modern civilization (155).

However, today it is recognised that individuals exhibit different susceptibilities to blood pressure increment from varying salt intake (156), hence the creation of the concept salt-sensitive or salt-resistant individuals. The mechanisms behind this phenomenon are as of today not fully understood but are likely based on a complex interaction of environmental factors with genetic modulation. Genetic studies have identified genes within RAAS as well as genes for the renal epithelial sodium channel (ENaC) associated with the susceptibility to salt induced hypertension (157, 158). Salt-sensitivity has been studied in subpopulations in the US, concluding a more pronounced effect from salt intake on the increase on blood pressure increase in the African American population (159).

Vascular ageing

As mentioned previously, age and ageing are strong risk factors for rising blood pressure, predominantly by structural changes in the arteries.

During the life course, the systolic blood pressure rises and diastolic blood pressure decreases, at least after 60-65 years, as the age increases, which has been attributed to increased arterial stiffness (160). There are several mechanisms contributing to the stiffening. As every heartbeat leads to stretching and relaxation of large elastic arteries, this gradually damages the arterial wall with depletion of elastin content and a relative increase of collagen in the arterial media (161). The process is also accelerated by hyperglycaemia and systemic inflammation (162, 163). The frequently used name for the changes is *arteriosclerosis*. A marker for these changes is increased pulse pressure (PP) (i.e. the difference between systolic and diastolic blood pressure) (164), which is easily obtained through blood pressure measurements. The blood pressure is commonly measured in the brachial artery, which is a muscular artery that is not exposed to arteriosclerosis to the same extent as large elastic arteries (aorta, carotids) (165). Hence, brachial PP underestimates the central PP leading to the necessity for other markers.

Pulse wave velocity

The most accepted biomarker for arterial stiffness is carotid-femoral 'pulse wave velocity' (PWV) (166). PWV is based on the assumption from physics on flow of an incompressible fluid, which in this case translates into a pulse wave travelling faster in a tube with rigid walls. Thus, increased stiffness results in an increased PWV. The mathematical model was described by Bramwell and Hill, which includes change in blood pressure (Δ P), change in blood volume (Δ V) and blood density (*p) (167).*

$$PWV = \sqrt{\frac{\Delta \mathrm{P} \times \mathrm{V}}{\Delta V \times p}}$$

The pulse waves are measured at two sites, and PWV is derived through the distance between measuring sites (ΔL, direct distance multiplied by 0.8 for approximating the true arterial distance and transit time (Δt) (168) Different techniques and localisations can be used. but the golden standard method is based on measurement in the right common carotid and right femoral artery, i.e. c-f PWV (6). This c-f PWV is described in m/s and a value exceeding 10 m/s is considered elevated (168).

The same device used for PWV measurements is usually able to retrieve central blood pressure through pulse wave analysis, performed at the *arteria radialis* via a transducer. PWV has been shown to be an independent predictor of cardiovascular

risk in meta-analyses, both in at-risk populations of patients and in the general population (169, 170). To exemplify, each increase of one m/s in PWV was shown to increase the risk for CVD events or all-cause mortality by around 15% (171).

The vascular ageing process takes a more rapid course in some individuals, which has been coined as Early Vascular Ageing (EVA), and was first described in 2008 and describing individuals with advanced arteriosclerosis already at a young age (172). The exact definition of EVA is however not fully established as of today, and the PWV thresholds to use for risk estimation is not agreed upon. In spite of this, the EVA concept could be an important future tool to identify high-risk subjects at an early stage.

Studies on ethnicity and PWV follow the consistent theme throughout this thesis, being mostly done in US settings on the African American population, concluding that this population exhibit increased PWV in comparison to Caucasians, even in a young normotensive population (173). The difference may be part explained by environmental factors such as lower socioeconomic status and unhealth behaviours resulting in obesity, both having a strong impact on increased stiffness (174). So far, studies have not been able to show any significant difference in genetic predisposition to increased arterial stiffness between ethnic groups (175) but it is most certainly a subject with knowledge gaps.

Diabetes

Diabetes pathophysiology and classification

Although not the main topic of this thesis, the fundamental characteristic for diabetes is elevated blood glucose levels (hyperglycaemia). The hormone insulin secreted from pancreatic beta-cells, but also peripheral or hepatic insulin resistance play immense roles in the pathogenesis of the disease through the impact on glucose regulation. For a long time, diabetes has been classified into two main categories: type 1 diabetes and type 2 diabetes. Type 1 diabetes is characterised by an auto-immune destruction of beta-cells rendering absolute insulin deficiency, but type 2 diabetes is multifactorial, mainly driven by a combination of impaired insulin action (or insulin resistance) and impaired insulin secretion. The pathophysiology is complex and affected by genetic, epigenetic, lifestyle and socioeconomic factors (176).

In 2008, the “All New Diabetics in Scania” (ANDIS) study was initiated, which includes patients in the Scania region in Sweden that are diagnosed with diabetes and followed for complications and is ongoing as of today.

In 2018, a seminal paper based on the ANDIS study suggested that diabetes is too heterogeneous to be divided only in two groups. In all, five subgroups of diabetes based on patient characteristics and risk of diabetic complications were defined (177). The included basic characteristics were 'age at onset of diabetes', 'BMI', 'HbA1c', 'estimate of β-cell function' (HOMA2-B), 'insulin resistance' (HOMA2-IR) and 'presence or absence of glutamic acid decarboxylase antibodies' (GADA). The main diabetes complications studied were CKD, retinopathy and stroke. The following new clusters were proposed:

- Cluster 1; *Severe autoimmune diabetes (SAID)*. Characterised by early-onset, low BMI, poor metabolic control, insulin deficiency and presence of GADA.
- Cluster 2; *Severe insulin-deficient diabetes (SIDD)*. Characterised by early onset, low BMI, low insulin secretion, poor metabolic control, GADA negative. Increased risk of retinopathy.
- Cluster 3; *Severe insulin-resistant diabetes (SIRD)*. Characterised by insulin resistance, high BMI. Increased risk of CKD.
- Cluster 4; *Mild obesity-related diabetes (MOD)*. Characterised by high BMI but not insulin resistance.
- Cluster 5; *Mild age-related diabetes (MARD).* Characterised by polder patients but only modest metabolic derangements.

Three other cohorts were used to replicate the clustering, the 'Scania Diabetes Register', the 'All New Diabetics in Uppsala', Sweden and the 'Diabetes Registry Vaasa', Finland (177)**.**

As of today, the contributing role of ethnicity to the new clusters has not been studied. Previous research has shown disparities in insulin sensitivity and insulin response depending on ethnicity. A meta-analysis from 2013 concluded that populations originating from Africa and East Asia have a more unbalanced relationship between insulin sensitivity and insulin response, in comparison to Caucasian subpopulations, making these groups more susceptible to diabetes (178). Further, the MEDIM-study has shown that in the Iraqi group, a large proportion of 'diabetes-free individuals' exhibit relative insulin deficiency as the insulin secretion could not compensate for the insulin resistance (179)

Cardiovascular diseases

The topics of this thesis – CKD, hypertension, arterial stiffness and diabetes are all strong risk factors for CVD - isolated, but often connected to each other. CVD includes coronary heart disease, peripheral vascular disease and cerebrovascular disease and is regarded to be the leading cause of death globally; the World Health Organisation (WHO) estimated that 32% of all deaths in 2019 could be attributed to CVD (180). The ethnic variation in CVD is well established – often showing an increased risk in various minority groups in Western countries. Part of the increased risk can be attributed to a clustering of traditional risk factors including lower socioeconomic status. However, in general, this just partly explains the increased risk. Hence, there are additional factors that remain to be unravelled (181, 182).

Aims

Overall aims

The *overall aim* of this thesis was to explore the contradictory findings that Middle Eastern immigrants exhibit more favourable blood pressure levels and display lower CVD risk than the native Swedish population, despite an accumulation of traditional cardiometabolic risk factors including diabetes. The aim was hence to explore potential differences across ethnicities in factors involved in the regulation of blood pressure and renal function, as well as on diabetes characteristics. This also aimed to enlighten the importance of a global perspective on health, which could further aid in developing a more individualistic and multi-ethnical approach in healthcare rendering greater health equity. The hypothesis was that differences exist in cardiometabolic risk factors and their regulating mechanisms across ethnicities.

Specific aims

Paper I: To study differences across Middle Eastern and European ethnicities in renal function and associations between renal function and blood pressure.

Paper II: To study differences across Middle Eastern and European ethnicities in diabetes traits and diabetes complications.

Paper III: To study differences across Middle Eastern and European ethnicities in associations between the biomarker Pro-Enkephalin (PENK) and renal function

Paper IV: To study differences across Middle Eastern and European ethnicities in renal function based on a golden standard method and validate equations for estimating renal function in the Middle Eastern population. Further, to study arterial stiffness by a golden standard method and to correlate it with renal function.

Subjects and Methods

This thesis is based on three research studies entitled the (a) MEDIM population-based study, (b) ANDIS-study and (c) the MEDIM 2019 population-based study, which are outlined in Table 3.

Table 3. Brief description of the studies used in the thesis.

	MEDIM	ANDIS	MEDIM 2019
Papers	I, III	II	IV
Year	2010-2012	2008-2016[1]	2019-2020
Eligble participants	Born in Iraq (n=1398) Born in Sweden (n=757)	Born in Iraq (n=286) Born in Sweden (n=10641)	Born in Iraq (n=31) Born in Sweden (n=32)
Design	Cross-sectional	Longitudinal follow-up	Cross-sectional
Primary outcomes	eGFR, blood pressure, PENK	Diabetes traits, diabetes complications	mGFR, eGFR, PWV
Statistical methods	Linear regression, logistic regression	Linear regression, logistic regresion, cox regression	Linear regression, logistic regression, bootstrapping.

[1]Is ongoing as of today, the years illustrate when participants were included for paper II.

Included studies and methodology

Paper I and III: The MEDIM population-based study

The MEDIM population-based study was initially carried out between 2010 and 2012 in Malmö, located in the southernmost part of Sweden. Malmö is Sweden's third largest city with as of 2020, around 35% of its population being born abroad. In 2015 the most common place of birth besides Sweden, was Iraq (1). The study recruited residents of Malmö between the ages of 30-75 years rendering a final study population of 2155 participants (Iraqi-born n=1398 and Swedish-born n=757). Exclusion criteria included physical and mental illness to an extent that made participation impossible. To reduce socioeconomic bias, the participants in both groups were recruited from the eastern residential areas of Malmö, which are in general more socioeconomically vulnerable. Invitations were sent out via mail with a response rate of 49% in the Iraqi-born group and 32% in the Swedish-born group. The participants took part in physical examinations, fasting blood sampling, oral glucose tolerance test and filled self-administered questionnaires on lifestyle habits,

social background, family history, medical history and drug medication use. The investigation was conducted by Swedish- and Arabic speaking research nurses.

Paper II: The ANDIS study

The ANDIS study is an ongoing longitudinal cohort study which begun 1st January 2008. It includes patients that are newly diagnosed with diabetes in the Scania region in Sweden which contains around 1 200 000 inhabitants. The participants in this study were included between the start on until 18 August 2016 and followed for CKD until 31 December 2016 and CVD until 5 April 2017. Inclusion criteria were individuals living in Skåne with newly diagnosed diabetes and born in either Iraq or Sweden. People with a duration of diabetes for more than two years were excluded. A total of 10 927 participants were finally included in the study (Iraqi-born n=286 and Swedish-born n=10641).

Fasting baseline blood samples were drawn upon inclusion. During follow-up, measurements for renal function (creatinine) were regularly updated from the clinical database at the Department of Clinical Chemistry, SUS Malmö.

The study population was included in the prior cluster analysis identifying the five novel subgroups of diabetes (177), thus no '*de novo*' cluster analysis was performed for this paper.

CKD was expressed as stage 3A eGFR <60 mL/min/1.73m^2 and stage 3B eGFR <45 mL/min/1.73m^2 for at least 90 days and captured from the regular updates from the clinical chemistry database. Diabetic retinopathy was defined as at least moderate retinopathy and a diagnosis was based on fundus photographs, assessed by experienced ophthalmologists. Coronary events included angina pectoris, ischaemic heart disease and atherosclerotic heart disease based on the diagnostic codes I20, I21, I24, I251 and I253-I259 as defined by the International Classification of Diseases (ICD-10). Stroke was defined by I60-I61 and I64-I64. Coronary events and stroke were captured through the National Patient Register, describing hospitalization or visits to hospital policlinics.

Genetic risk scores (GRS) were evaluated. The analyses used single nucleotide polymorphism (SNPs) identified in genome-wide association studies (GWAS), associated to type 2 diabetes (183), BMI (184), insulin secretion rate (ISR) (185) and insulin sensitivity index (ISI) (186). GRS was implemented in PLINK v1.9/2, an open-source GWAS analysis toolset.

Paper IV: The MEDIM 2019 population-based study

As a sub study to the original MEDIM-study, the MEDIM 2019 study was created to further investigate findings from the original one. It was conducted in Malmö,

Sweden, during 2019 to 2020. Due to the COVID-19 pandemic, it was put on hold in March 2020. The study recruited participants mainly from the original cohort, inviting individuals between the ages 30-65 years born in Iraq or Sweden. As the main aim for the study was to investigate the correlation between mGFR and eGFR, the initial participants were supposed to exhibit a normal renal function, hence the mentioned age interval, and following exclusion criteria; cardiovascular disease, known diabetes type 1 or type 2, chronic kidney disease (eGFR $<60mL/min/1.73m^2$), cardiovascular disease (myocardial infarction, stroke) and pregnancy. Due to the chemical characteristics of the iohexol clearance, untreated thyrotoxicosis, suspected thyroid cancer with the potential need for radioactive iodine or Myasthenia gravis acted as exclusion criteria as well.

Totally 350 randomly selected participants from the original MEDIM-study were invited by mail. Of these, 81 responded and were scheduled for a first inclusion visit which included oral and written information about the study, signed informed consent and a physical examination by a physician (CN). To improve the recruitment, also new participants, not originating from the original study, were also included, if the inclusion/exclusion criteria were met. These invitations were based on the original MEDIM participants spreading the word in the local community. An additional 23 new participants were recruited that were not original study participants.

Hence, a total of 104 participants attended the first inclusion visit. Sixty-three of them took part in the final visit. The drop-outs were mainly due to the COVID-19 pandemic that temporarily stopped the study in March 2020.

In between visits, blood samples were drawn to ensure correct design of iohexol clearance testing. At the main study day, blood samples were drawn, and each participant was physically examined by research nurses. Self-administered questionnaires in Swedish or Arabic were used to gather information on lifestyle, socioeconomic status and family history.

PWV and central blood pressure were measured by the tonometry apparatus 'SphygmoCor' (Atcor Medical, New South Wales, Australia). After five minutes of rest, each participant sat in the supine position. A pressure sensitive probe obtained pulse curves from the carotid and femoral arteries. Distance was measured from the suprasternal notch to the femoral artery - and from the suprasternal notch to the carotid artery. The latter was subsequently subtracted from the prior and multiplied by 0.8. At the same time, an electrocardiogram registered the time from the peak of the R wave to the foot of the pulse wave, at the carotid and femoral arteries. The results were then used together with the distance to calculate PWV. The aim was to achieve two successful measurements. The mean value of PWV was used in the final analyses. In addition, central systolic and diastolic blood pressure were automatically computed from arterial waveforms at the *arteria radialis*, by a transfer function.

Iohexol clearance was performed by using the non-iodine contrast agent Omnipaque^{TM} at the dosage 5ml (300 g I/ml). Omnipaque was injected through a peripheral venous catheter. At 180-, 200-, 220- and 240-minutes post injection, blood samples were drawn for measurement of iohexol concentration.

Six different eGFR equations were calculated from creatinine and/or cystatin C. These were chosen as they have been included in previous papers and are outlined in Table 4.

Table 4. Overview of the six different eGFR equations studied (paper IV)

	CKD-EPI$_{creatinine}$(105)	**CKD-EPI$_{cystatinC}$(187)**	**CKD-EPI$_{combined}$(188)**	**LMrev(108)**	**MDRD(189)**	**CAPA(109)**
First described	2009	2008	2008	2011	1999	2014
Original population	US, diverse renal function	US, diverse renal function	US, diverse renal function	Sweden, diverse renal function	US, CKD-patients.	Japanese adults, Swedish adults and children. Dutch children.
Clinical use	Globally, recomended by KDIGO	Globally, recomended by KDIGO	Globally, recomended by KDIGO	Standard method in Sweden	Globally but diminishing	Standard method in Sweden
Ethnicity adjustment	Yes (African American)	Yes (African American)	Yes (African American)	No	Yes (African American)	No

Laboratory Methods

Creatinine

All papers apart from **paper II** utilised creatinine measurements carried out at the Dept. Clinical Chemistry, Skåne University Hospital in Malmö. In **paper II**, blood samples were collected at various primary care health facilities in the Skåne region and creatinine was analysed at the different Clinical Chemistry departments in the Skåne region, which utilise the same apparatus and belong to the same main health care organisation.

All papers used an enzymatic colorimetric assay with an isotope dilution mass spectrometry (IDMS)-traceable calibrator on the Hitachi Modular P analysis system (Roche, Basel, Switzerland).

Cystatin C

Cystatin C was assessed in **paper I, III and IV**. The analyses were carried out at the Dept. Clinical Chemistry, Skåne University Hospital in Malmö. For **paper I, III,** cystatin C was determined from frozen blood samples from the original MEDIM study between 2010 and 2012. **Paper IV** used venous blood samples collected at the study visits for direct analyses. All papers used an automated particle-based

immunoassay, adjusted to the international reference preparation ERM-DA 471/IFCC, by the Hitachi Modular P analysis system (Roche) and reagents from DAKO (Glostrup, Denmark)

Pro-Enkephalin

Paper III assessed Pro-Enkephalin (PENK) as the main variable. Measurements were completed on frozen blood samples from the original MEDIM study in 2018 at SpingoTec GmbH (Henningsdorf, Germany). The analyses used a chemiluminometric sandwich immunoassay that utilises a stable solid phase and tracer antibodies for detection of endogenous fragments of the precursor Pro-Enkephalin A.

Albuminuria

In **paper IV** albuminuria was analysed in morning urine voids that were collected and directly analysed at the Dept. Clinical Chemistry, Skåne University Hospital in Malmö. Urine creatinine was measured by an enzymatic colorimetric assay with an IDMS-traceable calibrator on the Hitachi Modular P analysis system (Roche) in similarity to plasma creatinine. Measurement of urine albumin used an immunoturbidimetric assay on the Hitachi Modular P analysis system (Roche). Analyses were adjusted to the international reference preparation ERM-DA 471/IFCC. By urine creatinine and albumin, the ratio was calculated to the albumin-to-creatinine ratio (uACR).

Iohexol

The analyses at the Dept. Clinical Chemistry, Skåne University Hospital in Lund were done through protein precipitation by perchloric acid and then high-performance liquid chromatographic (HPLC) with UV detection at 245 nm. The four-sampling method (iohexol samples at 180, 200, 220 and 240 minutes after injection of iohexol was used and thereafter mGFR was computed by the Bröchner-Mortensen method (84).

Statistics

For statistical analyses, SPSS Statistics, version 23-25 (IBM, Armonk, New York, USA) and R were used. Through all papers, continuous data were presented as means (standard deviations; SD) if normally distributed. If not, data were presented as medians (interquartile ranges; IQR). Categorical variables were presented as numbers (percentage; %). When comparing continuous data across ethnicities, differences were calculated by linear regression models adjusted for age and sex. Differences between categorical variables (proportions) were calculated by logistic regression models adjusted for age and sex. Before linear regression analysis, non-normally distributed (skewed) variables were $\log_{10}$-transformed to approximate normal distributions. A p-value below 0.05 was considered significant.

Paper I and **III** used multivariate linear regression analysis to study associations between SBP/DBP and eGFR (**paper I)** and between eGFR and PENK (**paper III)**, adjusted for other cardiometabolic factors. As the mean values and standard distributions for continuous variables in these analyses differed in terms of ethnicity and sex. These variables were standardized within the strata of ethnicity and sex, i.e. z-scores. Both **paper I** and **III** utilized interaction analysis with the creation of interaction variables depending on country of birth ($P_{\text{interactinon=Country of birth x eGFRCAPA}}$ in **paper I** and $P_{\text{interactinon = Country of birth x PENK}}$ in **paper III**).

GRS analysis in **paper II** was done by logistic regression of z-score GRS in *R.* GRS were constructed in PLINK v1.9/2, by $r2$=0.1 and 250 kb window.

Hazard ratios (HR) with 95% confidence intervals (CI) for diabetic complications in **paper II** were calculated by Cox regression. For the evaluation of eGFR equations in **paper IV**. *Bias* was defined as the *median of the differences* between eGFR and mGFR (expressed in mL/min/1,73m^2) and as the *median percentage difference* between eGFR and mGFR in relation to mGFR (expressed in percent). *Precision* was determined by the interquartile ranges (IQR) of the difference between eGFR and mGFR. *Accuracy* was defined as percentages of eGFR within ±10% (P10) or ±30% (P30) of mGFR. Non-parametric 95% confidence intervals (CI) were calculated for medians (bias) and proportions (P10 and P30). CIs for bias used the bootstrapping methodology with 1000 replications.

Ethical considerations

Ethical permission for **paper I and III** was obtained as part of the MEDIM population-based study from the Regional Ethics Committee at Lund University (Dnr. 2009/36 and 2010/561). **Paper II** was approved as part of the ANDIS study by the Regional Ethics Committee at Lund University (Dnr.2006/584 and 2012/676). For **paper IV,** ethical permission was obtained from the Swedish Ethical Review Authority (2019-01141). For all papers, participants provided written consent before participation following information. The studies were compliant with the Declaration of Helsinki (190).

Results

Paper I

The total study population consisted of 2155 participants (1398 born in Iraq and 757 in Sweden). Individuals with a previous history of cardiovascular disease (stroke, myocardial infarction, angina pectoris) and individuals with missing values for eGFR due to laboratory limitations were excluded rendering a final study population of 1873 participants (1214 born in Iraq and 659 in Sweden).

Table 5. Characteristics of the study population (paper I)

	Born in Iraq. N=1214	**Born in Sweden n=659**	**p-value**
Age (years)[3,4]	45.0 (38.1-52.4)	48.7 (39.7-57.5)	**<0.001**
Male sex, n (%)[1]	722 (59.5)	353 (53.6)	**0.007**
BMI (kg/m^2)[2]	29.1 (4.3)	27.1 (4.5)	**<0.001**
SBP (mmHg)[2]	128.4 (16.4)	135.5 (19,7)	**<0.001**
DBP (mmHg)[2]	77.8 (10.2)	81.3 (11.4)	**<0.001**
Plamsa cystatin C (mg/L)[3,4]	0.87 (0.78-0.98)	0.88 (0.80-0.98)	0.052
Plasma creatinine (µmol/L)[2]	69.9 (15.4)	74.8 (14.3)	**<0.001**
$eGFR_{CAPA}$ (mL/min/1.73m^2)[3,4]	96.5 (82.6-108.4)	93.6 (80.3-105.7)	**0.009**
$eGFR_{LMrev}$ (mL/min/1.73m^2)[2]	102.6 (13.8)	94.3 (14.3)	**<0.001**
$eGFR_{Medel}$ (mL/min/1.73m^2)[2]	98.9 (15.6)	93.4 (15.0)	**<0.001**
$eGFR_{CKD\text{-}EPIcsystatin\ C}$ (mL/min/1.73m^2)[2]	93.6 (18,1)	91.3 (17,7)	**0.001**
$eGFR_{CKD\text{-}EPIcreatinine}$ (mL/min/1.73m^2)[3,4]	104.7 (94.4 – 112.1)	95.0 (83,8.104.6)	**<0.001**
Heart rate (beats/min)[2]	71.4 (9.8)	69.0 (11.2)	**<0.001**
Diabetes, n (%)[1,6]	109 (8.9)	34 (5.2)	**<0.001**
Waist circumference (cm), men[2]	99.1 (10.4)	97.3 (11.4)	**0.001**
Waist circumference (cm), women[2]	92.6 (10.3)	88.6 (13.7)	**<0.001**
Anti-hypertensive drugs, n (%)[1,5]	120 (9.9)	77 (11.7)	0.145
Self-reported hypertension, n (%)[1]	135 (11.1)	93 (14.1)	0.059
Alcohol consumers, n (%)[1]	217 (17.9)	552 (83.8)	**<0.001**
Active smokers, n (%)[1]	282 (23.2)	155 (23.5)	0.461
Physically active <150 min/week, n (%)[1]	857 (70.6)	221 (33.5)	**<0.001**
Often feeling stress in daily life, n (%)[1]	454 (37.4)	128 (19.4)	**<0.001**

Data are presented as numbers[1] (percentages) for categorical data, means[2] (standard deviations) or medians[3] (interquartile ranges) for continuous data. Non-normally distrubuted data were Log10-transformed[5] before comparison analysis. [5]Included ACE-inhibitors, ARB-antagonists, beta-receptor blockers, calcium antagonists and diuretics. [6]Defined as those with ongoing diabetes medication or positive oral glucose tolerance test.

The characteristics of the study population are presented in Table 5.

Blood pressure levels were lower among Iraqi-born immigrants. Renal function as measured by eGFR was better in the Iraqi group using both creatinine (LMrev-equation) and cystatin C (CAPA-equation) based measurements (102.6 vs. 94.3 mL/min/1.73m^2, p<0.001) and (96.5 vs. 93.6 mL/min/1.73m^2, p=0.009).

Stepwise linear regression showed that being born in Iraq was significantly associated with reduced risk of higher SBP when adjusted for several metabolic risk factors as outlined in Table 6.

Table 6. Factors associated with higher systolic blood pressure in the whole study population (paper I)

	β	95% CI
Age	**5.61**	**4.75 – 6.47**
Country of birth (Iraq)	**-7.41**	**-8.83 - -5.99**
Sex (female)	**6.41**	**5.04 – 7.78**
$eGFR_{CAPA}$	**-2.75**	**-3.49 - -2.00**
Diabetes	1.53	-1.16 – 4.29
BMI	**4.47**	**3.74 – 5.20**
Heart rate	**2.46**	**1.75 – 3.17**

Multivariate regression analysis with dependent variable systolic blood pressure. Expressed as β (beta)-values with 95% confidence intervals. Significant data is bolded and implied by confidence intervals above or below zero. Continous data were standardised within the strata of ethnicity and sex (z-scores).

The relationship between $eGFR_{CAPA}$ and systolic blood pressure is presented in Figure 4 illustrating a less steep line in the Iraqi group indicating a weaker association between eGFR and systolic blood pressure in this group.

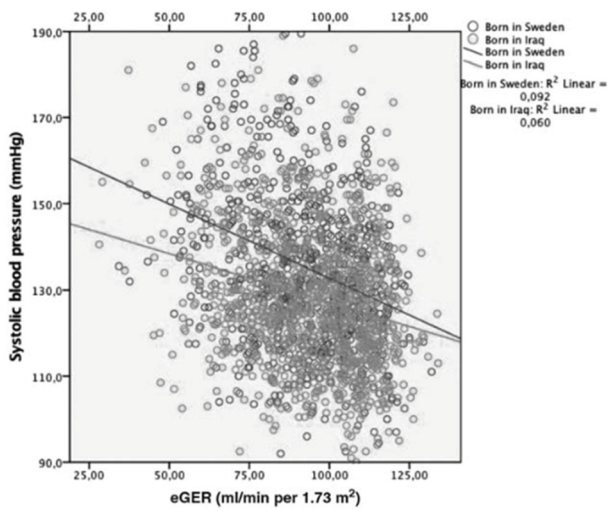

Figure 4: Relationship between systolic blood pressure and eGFR. From Nilsson C *et al* (191)

Subsequently, to determine whether there existed a significant modifying effect of ethnicity on renal function in relation to blood pressure - an interaction variable was created ($P_{\text{interactinon=Country of birth x eGFRCAPA}}$). In linear regression, the interaction term was significant ($P_{\text{interactinon=Country of birth x eGFRCAPA}}$=0.004**)**, which indicates that the association between renal function and blood pressure differs depending on country of birth. The interaction term remained significant also when adjusting for BMI ($P_{\text{interactinon=Country of birth x eGFRCAPA}}$=0.011). When using $eGFR_{CKD\text{-}EPIcystatinC,}$ the interaction term remained significant ($P_{\text{interactinon=Country of birth x eGFRCKD-EPIcystatinC}}$=0.001), hence the relationship was not dependent on a specific equation.

Paper II

The initial study population consisted of 10927 participants (286 born in Iraq and 10641 born in Sweden). Due to missing data, the final study population consisted of 7227 participants (183 born in Iraq and 7044 born in Sweden).

Characteristics are presented in Table 7.

	Born in Iraq. N=183	**Born in Sweden n=7044**	**p-value**
Age at diagnosis (years)[2]	51.4 (10.4)	61.2 (12.5)	**<0.001**
Men, n (%)[1]	130 (71)	4218 (59.9)	**0.025**
BMI (kg/m^2)[2]	30.6 (5.1)	30.6 (5.7)	0.060
Hypertension, n (%)[1]	83 (45.4)	5125 (72.9)	**<0.001**
HbA1c (mmol/mol)[2,3]	66.9 (25.6)	62.7 (24.8)	0.656
C-peptide, (nmol/L)[2,3]	1.1 (0.4)	1.3 (0.6)	0.984
HOMA2-β[2,3]	84.7 (45.1)	90.7 (45.7)	0.203
HOMA2-IR[2,3]	2.8 (1.4)	3.3 (1.9)	0.067
GADA positive, (n (%)[1]	4 (2.2)	496 (7.0)	**0.001**
GADA concentration (kE/L)[2]	148.3 (117.7)	159.6 (105.1)	0.977
$eGFR_{MDRD}$ (mL/min/1.73m^2)[2]	107.1 (27.6)	90.1 (24.9)	**<0.001**
Chronic kidney disease, n (%)[1]			
eGFR <60 mL/min/1.73m^2	1 (0.5)	448 (6.4)	0.184
eGFR <45 mL/min/1.73m^2	-	111 (1.6)	0.995

Data are presented as numbers[1] (percentages) for caterogircal data or means[2] (standard deviations) for continuous data. Linear regression (continious variables) or logistic regression (categorical variables) were used for comparisons between the groups adjusting for sex, age at diagnostis and BMI. Non-normally distributed data were Log10-transformed[3] before comparison analyses.

Renal function was better in the Iraqi group at baseline (107.1 vs 90.1 mL/min/1.73m^2, p<0.001). In addition, hypertension was less prevalent in the Iraqi group (45.4 vs. 72.9%, p<0.001).

The distribution of diabetes clusters is presented in Figure 5. In the Iraqi group, the most prevalent diabetes subgroup was MOD followed by SIDD. The other clusters MARD, SIRD and SAID were however, less prevalent in the Iraqi group.

The genetic risk score (GRS) analysis showed that the Iraqi group had higher GRS for type 2 diabetes (OR 1.19, 95% CI 1.046 – 1.353, p<0.001) and lower risk for insulin resistance (1.179, 1.035-1.343, p=0.013). GRS was lower for BMI (0.828, 0.726-0.944, p<0.001) and insulin secretion rate (0.729, 0.643-0.827, p<0.001) meaning higher genetic variants load associated with impaired insulin secretion.

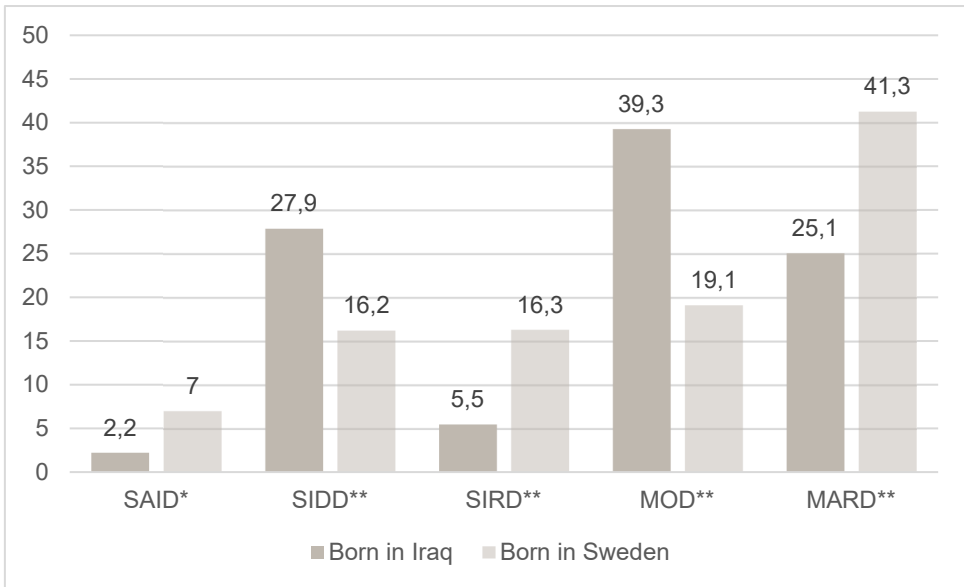

Figure 5: Distribution (%) of five novel diabetic subgroups in patients with diabetes born in Iraq or Sweden. *=0.016.**<0.001. SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; MOD, mild obesity-related diabetes; MARD, mild age-related diabetes.

Table 8: Cox regression of hazard ratios (HR) with 95% confidence intervals (CI) for coronary events and chronic kidney disease during follow up (paper II).

	HR	95% CI	HR	95% CI
Coronary events				
Country of birth (Sweden ref)	1.56	0.91 – 2.69	**1.84**	**1.06-3.12**
Age at onset (years)	**1.04**	**1.03-1.05**	**1.04**	**1.03-1.05**
Sex (male sex ref)	**0.42**	**0.34-0.52**	**0.41**	**0.32-0.51**
BMI (kg/m^2)	0.99	0.97-1.01	0.99	0.97-1.01
HbA1c (mmol/mol)			1.00	0.99-1.01
Chronic kidney disease				
Country of birth (Sweden ref.)	**0.26**	**0.08-0.8**	0.30	0.074-1.20
Age at onset (years)	**1.10**	**1.09-1.11**	**1.05**	**1.04-1.06**
Sex (male sex ref)	**1.29**	**1.15-1.44**	1.07	0.94-1.22
BMI (kg/m^2)	**1.03**	**1.02-1.04**	1.02	1.01-1.03
HbA1c (mmol/mol)			**1.01**	**1.00-1.01**
eGFR at baseline (mL/min/1.73m^2)			**0.93**	**0.92-0.93**

Hazard ratios with confidence intervals. Significant data is bolded and implied by confidence intervals above or below zero.

During the follow-up, two participants born in Iraq and 955 participants born in Sweden were recorded with chronic kidney disease stage 3A (<60 ml mL/min/1.73m^2) The risk was significantly lower among the Iraqis as illustrated in Table 8. The trend remained when adjusted for baseline eGFR, but no longer significant. In addition, during follow-up 14 participants born in Iraq and 376 participants born in Sweden were recorded with coronary events. The risk was significantly higher among the Iraqis.

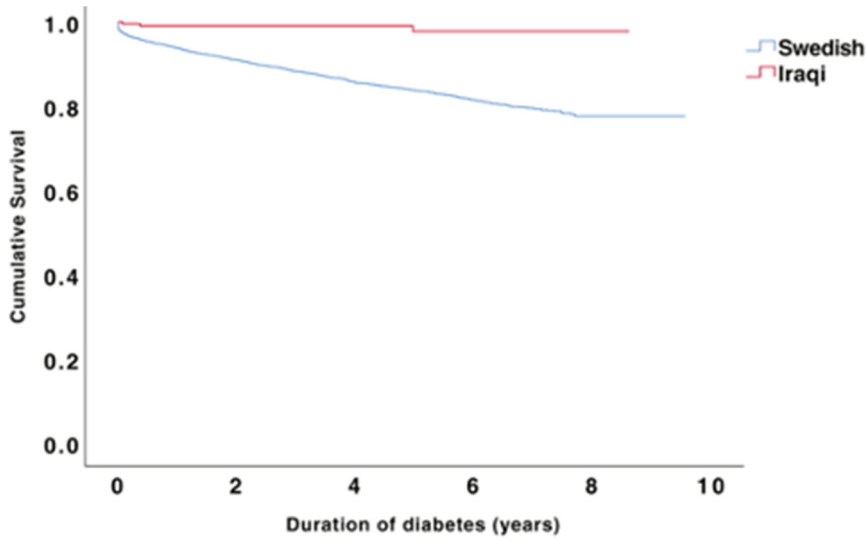

Figure 6: Development of CKD 3A (eGFR <60 mL/min/1.73m^2 during follow-up in diabetes patients born in Iraq or Sweden. From Bennet *et al* (192).

Paper III

The initial study population consisted of 2155 participants (1398 born in Iraq and 757 in Sweden). Due to laboratory errors, Pro-Enkephalin (PENK) could not be analysed in some of the samples rendering a final study population of 1952 participants (1263 born in Iraq and 689 in Sweden)

Table 9. Characteristics of the study population (paper III).

	Born in Iraq. N=1263	Born in Sweden n=680	p-value
Age (years)[3,4]	45.0 (38.3-52.7)	48.7 (39.6-57.9)	**<0.001**
Men, n (%)[1]	756 (59.9)	370 (53.7)	**0.009**
PENK (pmol/L)[2]	70.0 (18.2)	71.1 (17.8)	0.432
SBP (mmHg)[2]	128.9 (16.5)	135.4 (19.9)	**<0.001**
DBP (mmHg)[2]	77.9 (10.3)	80.9 (11.6)	**<0.001**
Plamsa cystatin C (mg/L)[3,4]	0.88 (0.79-0.98)	0.89 (0.80-0.99)	**0.047**
Plasma creatinine (µmol/L)[2]	70.3 (15.8)	74.9 (14.2)	**<0.001**
$eGFR_{CKD\text{-}EPIcystatin\ c}$ (mL/min/1.73m^2)[2]	93.6 (18.1)	91.4 (17.9)	**0.001**
$eGFR_{CKD\text{-}EPIcreatinine}$ (mL/min/1.73m^2)[3,4]	104.8 (94.2-112.2)	95.0 (83.9-104.5)	**<0.001**
BMI (kg/m^2)[2]	29.1 (4.3)	27.2 (4.5)	**<0.001**
Diabetes, n (%)[1,6]	136 (10.8)	33 (4.8)	**<0.001**
Anti-hypertensive drugs, n (%)[1,5]	152 (12.0)	102 (14.8)	0.077
Active smokers, n (%)[1]	303 (24.0)	171 (24.8)	0.514

Data are presented as numbers[1] (percentages) for caterogircal data, means[2] (standard deviations) or medians[3] (interquartile ranges) for continuous data. Linear regression (continious variables) or logistic regression (categorical variables) were used for comparisons between the groups adjusting for sex and age. Non-normally distributed data were Log10-transformed[4] before comparison analyses. [5]Included ACE-inhibitors, ARB-antagonists, beta-receptor blockers, calcium antagonists and diuretics. [6]Defined as those with ongoing diabetes medication or positive oral glucose tolerance test.

The characteristics were similar as for **paper I** with the Iraqi group being younger and more often men. Renal function as described previously was better in the Iraqi group. Levels of PENK did not differ between the groups (70.0 vs. 71.1 pmol/L, p=0.432).

The following analysis used $eGFR_{CKD\text{-}EPIcreatinine}$ as determinant for eGFR.

In regression analysis higher eGFR was associated with younger age, female sex, lower prevalence of diabetes, systolic blood pressure and lower levels of PENK as illustrated by the linear regression model in Table 10.

Table 10. Factors associated with higher levels of $eGFR_{CKD\text{-}EPIcreatinine}$ (paper III).

	β	95% CI
Age	**-0.57**	**4.75 – 6.47**
Country of birth (Iraq)	**0.53**	**0.45 – 0.60**
Sex (male)	**-0.33**	**-0.40 - -0.26**
PENK	**-0.23**	**-0.26 - -0.19**
Diabetes	**0.04**	**0.000 – 0.09**
SBP	**-0.04**	**-0.08 - 0.00**

Multivariate regression analysis with dependent variable $eGFR_{CKD\text{-}EPIcreatinine}$.Expressed as β (beta)-values with 95% confidence intervals. Significant data is bolded and implied by confidence intervals above or below zero. Continous data were standardised within the strata of ethnicity and sex (z-scores).

To further study whether the relationship between eGFR and PENK differed depending on country of birth, an interaction term was created ($P_{interactinon=\ Country\ of\ birth\ x\ PENK}$), which was significant (p=0.031) in linear regression analysis with eGFR as dependent variable adjusted for age, sex, diabetes and SBP, indicating a weaker relationship between eGFR and PENK as illustrated by Figure 7.

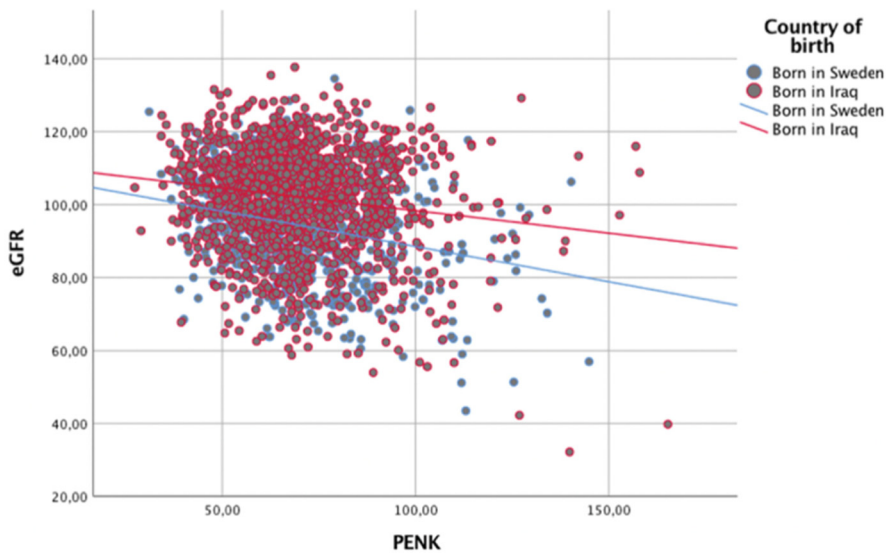

Figure 7: Relationship between PENK and eGFR. From Nilsson C *et al* (193).

Paper IV

The initial study population consisted of 63 participants (31 born in Iraq and 32 born in Sweden). Due to laboratory errors, analyses based on mGFR included 61 participants (29 born in Iraq and 32 born in Sweden). Characteristics are presented in Table 11.

Table 11. Characteristics of the study population (paper IV).

	Born in Iraq. N=31	**Born in Sweden n=32**	**p-value**
Age (years)[2]	48.3 (7.4)	52.1 (8.9)	0.373
Men, n (%)[1]	17 (54.8)	15 (46.9)	0.057
SBP (mmHg)[3,4]	133.5 (117.5-139.5)	125.0 (117.0-140.0)	0.355
DBP (mmHg)[3,4]	83.0 (72.0-91.0)	74.5 (70.5-85.0)	**0.018**
Plamsa cystatin C (mg/L)[3,4]	0.82 (0.77-0.91)	0.90 (0.75-0.96)	0.633
Plasma creatinine (µmol/L)[2]	64.1 (13.0)	72.3 (13.5)	**0.001**
PWV (m/s)[2]	7.7 (1.1)	8.0 (1.0)	0.658
Central SBP (mmHg)[3,4]	119 (108.0-126.0)	116.5 (104.5-127.0)	0.552
Central DBP (mmHg)[3,4]	82.0 (74.0-91.0)	75.5 (71.0-85.5)	**0.031**
uACR > 3g/mol, n (%)[1]	6 (19.3)	1 (3.1)	0.065
Heart rate (beats/min)[2]	66.5 (10.3)	62.2 (8.4)	0.104
BMI (kg/m^2)[2]	30.2 (4.5)	26.9 (5.2)	**0.011**
Anti-hypertensive drugs, n (%)[1]	8 (25.8)	7 (21.9)	0.217
Active smokers, n (%)[1]	6 (19.3)	4 (12.5)	0.316
Alcohol consumers, n (%)[1]	5 (16.1)	27 (84.3)	**0.013**
Waist circumference (cm), men[3,4]	106.0 (95.5-109.0)	100.0 (93.0-110.0)	0.405
Waist circumference (cm), women[3,4]	88.0 (84.8-101.8)	85.0 (75.5-92.5)	**0.031**

Data are presented as numbers[1] (percentages) for caterogircal data, means[2] (standard deviations) or medians[3](interquartile ranges) for continuous data. Linear regression (continious variables) or logistic regression (categorical variables) were used for comparisons between the groups adjusting for sex and age. Non-normally distributed data were Log10-transformed4 before comparison analyses.

Somewhat surprisingly, both brachial and central DBP were higher in the Iraqi group, although the differences did not remain significant when adjusted for BMI (p=0.061 for brachial DBP), and p=0.062 for central DBP). As in previous papers, BMI levels were higher in the Iraqi group as well as lower rate of alcohol use. Albuminuria was more prevalent in the Iraqi group but did not a reach level of significance.

Table 12. mGFR and eGFR (mL/min/1.73m^2) based on six different eGFR equations for renal function (paper IV).

	Born in Iraq n=29	**Born in Sweden n=32**	**p-value**
mGFR	101.0 (88.0-106.5)	85.5 (80.25-104.5)	0.2
CKD-EPI$_{creatinine}$	107.0 (101.0-110.5)	94.5 (80.25-102.75)	**<0.001**
CKD-EPI$_{Cystatin\ c}$	100.0 (88.5-108.5	88.5 (79.25-104.76)	0.5
CKD-EPI$_{combined}$	104.0 (97.5-111.5)	92.0 (82.0-104.25)	**0.028**
LMrev	97.0 (89.5-102.5)	85.0 (75.0-85.0)	**0.001**
MDRD	105.0 (93.5-115.5)	83.5 (73.25-100.0)	**<0.001**
CAPA	94.0 (84.0-100.0)	84.5 (79.0-105.75)	0.8

All data are presented as medians (interquartile ranges). Linear regression was used for comparisons between the groups adjusting for sex and age. As all data were non-normally distributed, they were Log10-transformed before comparison analyses.

As seen in Table 12. mGFR did not significantly differ between the groups. All creatinine-including equations (CKD-EPI$_{Creatinine}$, CKD-EPI$_{Combined}$, LMrev and MDRD) showed significantly higher levels of eGFR in the Iraqi group. The cystatin C including equations (CKD-EPI$_{cystatinC}$ and CAPA) did not differ.

In Table 13, three different metrics for the performance of the eGFR equations are presented. As illustrated by the median difference, CKD-EPI$_{creatinine}$ overestimated eGFR in comparison to mGFR in the Iraqi group while LMrev underestimated eGFR in the Swedish group. The other equations did not show any significant under- or overestimation (i.e. CI below or above zero)

CAPA was the only equation showing a significant difference in bias (median percentage difference) between the groups (no overlap in confidence interval). No equation had a significantly median percentage value below 10% which is clinically regarded as a threshold for an acceptable bias.

In precision analysis, all equations exhibited significant P30 values above 75% except CAPA in the Iraqi group.

Table 13. Metrics for performance of six GFR equations in comparison to mGFR (paper IV).

	Born in Iraq. N=29	**Born in Sweden n=31**
Bias – Median difference[1]		
$CKD\text{-}EPI_{creatinine}$	**4.0 (2.4 – 11.7)**	0.5 (-2.1 – 5.4)
$CKD\text{-}EPI_{Cystanin\ C}$	-2.0 (-5.2 – 4.8)	1.0 (-2.2 – 4.4)
$CKD\text{-}EPI_{combined}$	3.0 (-4.3 – 9.5)	2.5 (-0.5 – 5.2)
LMrev	-6.0 (-7.5 – 2.2)	**-7.5 (-9.5 - -1.6)**
MDRD	6.0 (-0.7 – 12.2)	-7.0 (-8.5 – 1.2)
CAPA	-8.0 (-10.8 – 1.7)	-2.0 (-4.5 – 2.0)
Bias - Median Percentage difference[2]		
$CKD\text{-}EPI_{creatinine}$	8.6 (7.9-17.1)	8.4 (7.6-13.6)
$CKD\text{-}EPI_{Cystanin\ C}$	9.4 (9.3-16.7)	6.9 (6.4-11.1)
$CKD\text{-}EPI_{combined}$	8.7 (8.6-16.5)	7.5 (6.2-10.4)
LMrev	11.5 (9.3-14.2)	10.3 (8.6-13.8)
MDRD	12.9 (12.0-21.3)	10.6 (8.9-16.6)
CAPA	13.4 (11.8-19.1)	6.6 (6.2-10.6)
Precision – Interquartile ranges (IQR)[3]		
$CKD\text{-}EPI_{creatinine}$	15.5 (4.0-19.5)	9.0 (5.0-14.0)
$CKD\text{-}EPI_{Cystanin\ C}$	13.5 (5.5-19.0)	7.5 (4.0-11.5)
$CKD\text{-}EPI_{combined}$	16.5 (4.0-20.5)	5.75 (3.25-9.0)
LMrev	11.5 (6.0-17.5)	11.75 (4.25-16.0)
MDRD	16.0 (6.5-22.5)	14.5 (4.0-18.5
CAPA	10.5 (8.5-19.0)	7.0 (4.0-11.0)

[1]Expressed as mL/min/1.73m^2 with 95% confidence intervalls. Significant data is bolded and implied by confidence intervals above or below zero. [2]Expressed as percentages (%) with 95% confidence intervalls. [3]Expressed as mL/min/1.73m^{2}with interquartile ranges.

Table 14. Accuracy of six eGFR equations in comparison to mGFR (paper IV)

	$CKD\text{-}EPI_{creatinine}$	**$CKD\text{-}EPI_{cystatinC}$**	**$CKD\text{-}EPI_{combined}$**	**LMrev**	**MDRD**	**CAPA**
Born in Iraq						
P10, n (%)	55.2 (35.7-73.6)	48.3 (29.4-67.5)	51.7 (32.5-70.6)	44.8 (26.4-64.3)	34.5 (17.9-54.3)	31.0 (15.3-50.8)
P30, n (%)	100 (88.1-100.0)	93.1 (77.2-99.2)	100 (88.1-100.0)	100 (88.1-100.9)	96.6 (82.2-99.9)	82.8 (64.2-94.2)
Born in Sweden						
P10, n (%)	53.1 (34.7-70.1)	56.3 (37.6-73.6)	75.0 (56.6-88.5)	43.8 (26.4-62.3)	43.8(26.4-62.3)	68.8 (50.0-83.9)
P30, n (%)	100 (89.1-100.0)	100 (89.1-100.0)	100 (89.1-100.0)	96.9 (83.8-99.9)	93.8 (79.2-99.2)	96.9 (83.8-99.9)

Expressed as percentages of eGFR within ±10% or ±30% of mGFR with 95% confidence intervalls.

Discussion

This thesis investigates a specific population, Iraqi-born residents of Sweden, acting as a proxy for the wider Middle Eastern immigrant population. The populations in the Middle East share many similarities regarding lifestyle habits, culture, language and religion. It should, however, be pointed out that variations exist between the countries, especially for development status. Furthermore, Iraq is an ethnically divided country, which should be kept in mind when interpreting the results.

This thesis explores predominantly renal function, but also adjacent themes, including blood pressure, diabetes and CVD, which in many ways are strongly intertwined. The following discussion is divided into five parts on the specific themes and subsequently a general discussion on potential mechanisms and so forth.

Blood pressure and hypertension

Paper I and **III** based on the original MEDIM study showed a clear advantage in the Iraqi group with lower systolic as well as diastolic blood pressure despite higher BMI, larger waist circumference and less physical activity. Especially high BMI is considered to be strongly associated with increased blood pressure (194), hence the results are surprising. It has been previously described that the association between blood pressure and BMI is weaker in the Iraqi group (15). Age is considered as one of the strongest risk factor for hypertension (150). The fact that the Iraqi group was younger with a difference in median age of 3.7 years in the original MEDIM study, may suggest that part of the more favourable blood pressure profile in the Iraqi group, could thus be attributed to the younger age. Although, the significant disparity remained also when age-adjusted, indicating a "true" advantage.

Although we had no information on specific blood pressure levels, **paper II** showed a lower prevalence of self-reported hypertension in the Iraqi group. The more favourable blood pressure profile of the Iraqi group is consequently seen in two different studies, strengthening the results. As illustrated by several examples in the introductory section "Research on Middle Eastern immigrants", the finding that Middle Eastern immigrants in Western countries exhibit a more favourable blood pressure profile is shown in several cohorts and countries (5, 8, 9), strengthening these results as well. In summary, this suggests that Middle Eastern immigrants do exhibit a more favourable blood pressure profile in general.

Surprisingly and contradictory, **paper IV** showed higher unadjusted diastolic blood pressure levels in the Iraqi group. Other characteristics including age and BMI in this paper resembles characteristics of study participants in the other papers. Thus the result cannot be explained by a selection bias. It is noteworthy that the significance disappeared when adjusting for BMI. Considering the previously mentioned "healthy migrant effect (28)" that usually decreases over time - the participants born in Iraq in **paper IV** have been living considerably longer in Sweden than study participants in the other papers. One theory may consequently be that the healthy migrant effect during the first years in a new country could at least partly explain the more favourable blood pressure profile in **papers I, II** and **III.** The low number of participants could contribute to insufficient statistical power which should be considered before reaching firm conclusions.

Arterial stiffness (PWV) was included in **paper IV.** PWV did not differ between the groups. Most previous studies on PWV have been performed in substantially larger study groups and therefore this study population from MEDIM should be expanded in the future. With the lower blood pressure profile and studies pointing towards a lower CVD risk in the Iraqi group – it is plausible that this could translate into lower levels of PWV, a hypothesis still to be proven.

The main findings in **paper I** was the better renal function and the weaker association between blood pressure levels and renal function in the Iraqi group. The long-term relation between these two entities is well established, as higher blood pressure predicts to impaired renal function in the future (195). The association as measured at a specific moment in time is more unclear. A Norwegian study from 2010 explored the relationship between mGFR and ABPM, in a general population showing that increase in ABPM, was associated with reduced GFR in both normotensive and hypertensive subjects (196). It is debatable which way the direction goes in such an association, renal impairment rendering hypertension - or does elevated blood pressure damage the kidneys. Hence, there are uncertainties on how to exactly interpret the findings, although it supports a hypothesis describing different blood pressure and renal function regulation in the Iraqi group that seems to be of protective advantage.

Renal function

The better renal function among Iraqis described in **papers I** and **III** is a snapshot in time. There are pitfalls in drawing too firm conclusions in cross sectional comparisons, especially for subjects with in general, normal eGFR values.

The laboratory imprecision for the creatinine analyses was 1.4% and 2.1% for cystatin C analyses. Hence, the lab method should be analytically reliable with such low variance. Studies on within-individual variations have shown variations of 5.8% for serum creatinine and 5.4% for cystatin C (197). The variations increase with

impaired renal function (198). Thus, the single sampling procedure as determinant of renal function renders some insecurity to the results. Optimally, renal markers should have been measured repeatedly with mean values used as the primary determinant.

However, **paper II** shows both higher eGFR at baseline, and a lower progression rate to CKD in the setting of diabetes in the Iraqi group, during follow-up, which could be seen as an indication of a persisting renal function advantage in this group, at least in the setting of diabetes. It would of course be of much interest to have recorded eGFR values for all participants in **paper II** at the end of follow-up, to further explore this topic. **Paper IV** explores renal function around 7-10 years after the initial study sample collection for **papers I** and **III** with a majority of the participants recruited from the initial MEDIM population. The results are somewhat varying dependent on choice of GFR estimation, but renal function was significantly better despite a low number of study participants in the Iraqi group for four of the used equations, further strengthening the assumption of a more favourable renal function in the Iraqi group. Measured GFR through iohexol clearance did not differ significantly between the groups, which presumably is sample size dependent.

The more favourable renal function in the Iraqi group is thus shown in three different cohorts at different times, which is a strength. Other studies on renal function in this immigrant group are sparse. As outlined previously, epidemiology of CKD in the Middle East is associated with great uncertainties, rendering this a topic of novelty but also of uncertainties. Although crude eGFR values provide valuable information, a perspective of possibly even more interest would be to longitudinally investigate the renal function at baseline in **papers I** and **II** against **paper IV** for the individuals participating in both studies, preferably after inclusion of additional participants.

In similar fashion, as the renal function is measured isolated at one time, it could be argued that the enhanced renal function at baseline in the Iraqi group, considering their increased diabetes prevalence - is a proxy for glomerular hyperfiltration, i.e. a supraphysiologic elevation in GFR early in the course of diabetes (199). The lower risk for CKD among Iraqis in **paper II** is a counterargument against that hypothesis. This could be better elucidated by a longitudinal follow-up study as outlined above.

It is of interest that manifest albuminuria showed a trend to be more prevalent in the Iraqi group although nonsignificant in **paper IV**. Unfortunately, information on albuminuria is lacking in **papers I, II** and **III.** Albuminuria is a strong predictor of future decline in renal function (200). Few studies have explored the impact of ethnicity on albuminuria but in 2010 it was discovered that American Indians/Alaska Natives without traditional risk factors such as hypertension and diabetes, had higher risk for albuminuria in a population with eGFR above 60 mL/min/1.73m^2 (201). It has further been shown that in high-risk populations for diabetes, the presence of albuminuria is a predictor of a future diabetes diagnosis

(202). Incident albuminuria may thus be a reflection of the increased risk for diabetes in the Iraqi group but should of course be studied on larger cohorts. Albuminuria and the longitudinal risk of CKD may be a topic of research, particularly considering the lower CKD risk among Iraqis with diabetes as seen in **paper II.**

Assessment of renal function

The uncertainties in the choice of renal function measurement goes like a red thread through the thesis, hence the development of **paper IV.** In **paper I,** the CAPA equation for cystatin C and LMrev equation for creatinine were chosen as primary determinants. For uniformity purposes, CKD-EPI based eGFR was also added to the thesis results.

The rationale behind choosing CAPA and LMrev was the recognised accuracy and well-established usage of these methods in Sweden. **Paper III** was somewhat more speculative and hypothesis-generating. As PENK is still an emerging biomarker, it was of importance to adapt the study to previous research. In this case, previous studies on PENK have predominantly used creatinine measurements (133, 134), leading to the use of the widely recognized $CKD\text{-}EPI_{creatinine}$ as primary variable in this paper.

Papers I and **III** explores these equations in a study group based on the same population, although the exact study population differs between the papers due to laboratory errors and differences in inclusion criteria.

In both papers**,** all eGFR estimates are significantly higher in the Iraqi group. As the estimates differed in skewness, they are not uniformly described, since both means, and medians are used. Thus, straight crude comparisons between eGFR levels depending on equations, should be done with caution in these papers. Though by looking at the descriptive data, both cystatin C including equations ($eGFR_{CAPA}$ and $GFR_{CKD\text{-}EPIcystatinC}$) exhibit a reduced difference in comparison to the creatinine including equations ($eGFR_{LMrev}$ and $eGFR_{CKD\text{-}EPIcreatiine}$). The difference between the groups also looks rather similar when comparing both cystatin C including equations and creatinine-including equations. The main finding on renal function in these two papers should thus be that, independent which eGFR equation is chosen, the baseline renal function was superior in the Iraqi group.

To make it even more complicated, **paper II** instead utilises the MDRD equations, which is decreasing its clinical importance. The ANDIS study began in 2008 and was designed before the introduction of the CKD-EPI equation, as well as the CAPA- and LMrev equation which have been developed since 2010. As it is widely recognised that the mentioned equations outperform the MDRD equation (106, 203, 204), it would of course be optimal to present eGFR based on some of these equations in addition. Although, if not solely looking at crude eGFR levels, it should

be reliable enough to study the difference between the two groups, which is clearly significant. A potential objection to this might be that the MDRD equation is shown to overestimate CKD risk among African Americans, while underestimate it among white individuals (205), thus, the lack of validation in Middle Eastern populations may affect the primary outcome of the paper - the lower progression to CKD in the Iraqi group. Although this reasoning could also speak in the other direction, that even additional subjects in the Swedish-born group should have been diagnosed with CKD, considering the risk of underestimation known in this ethnic population.

Hence **paper IV –** designed to investigate six different eGFR equations that were included in the previous papers. Unfortunately, due to the COVID-19 pandemic, the study was paused, rendering fewer participants than expected. A pre-study power calculation indicated the need of a study population consisting of 95 Iraqi-born and 95 Swedish-born. Hence, the final study population of 29 and 32 participants, respectively, is too small. We hope to resume the study in the future then the pandemic is over. Consequently, the results should be interpreted with caution and for the most part be seen as indicative.

For *accuracy,* a P30 of >75% is generally regarded as satisfactory (206). In the Swedish group, all equations exhibited this trait. In the Iraqi group, the CAPA equation failed to meet the requirements. All other equations were sufficient in terms of accuracy.

An acceptable *bias* is considered as a median percentage difference of <10% (207). As illustrated in Table 13 in **paper IV**, no estimates had confidence intervals below 10%, i.e. no equation was significantly non-biased in any of the groups. This is presumably mostly an effect caused by the small sample size, as these equations have been previously studied in Swedish populations exhibiting good results. Of interest, the only equation exhibiting a significant difference in median percentage between the groups, was the CAPA equation, which raises some question on the findings in **paper I**, which utilised eGFR based on CAPA as the main variable. It should be noteworthy that the differences in eGFR between the groups are similar when using either $eGFR_{CAPA}$ or $eGFR_{CKD\text{-}EPIcystatinC}$ in **paper I**. Hence the main conclusions from that paper should be reliable as the significant interaction term was repeated using $eGFR_{CKD\text{-}EPIcystatinC}$.

In summary for the crude median differences, the LMrev equation underestimated eGFR in comparison to mGFR in the Swedish group and $CKD\text{-}EPI_{Creatinine}$ overestimated eGFR in the Iraqi group.

No significant differences between the groups in crude median differences existed for any of the other equations.

Altogether, the results are not conclusive, mainly due to the limited sample size rendering difficulties in analysing. The study is, however, indicative and propose potential disparities in eGFR estimation between the two groups. As the CAPA

equation was the only equation to significantly show inconsistencies (i.e. inaccuracy in terms of P30 values in the Iraqi group and significant difference in bias between the groups), this might suggest that the CAPA equation and cystatin C should be used with caution among Middle Eastern immigrants. The ambition is that the investigated study populations should be expanded.

Pro-Enkephalin

There is still much to be discovered about the biomarker PENK. As it is proposed to exhibit a direct mechanistic effect on the kidneys (139), it distinguishes itself among biomarkers, and was therefore chosen for this thesis. In the following section, PENK should be considered as a proxy for enkephalins.

The direction for the relationship between PENK and renal function is somewhat ambiguous. As PENK is proposed to induce a diuretic and natriuretic response (208), one can hypothesise that PENK increases as a counter-regulatory mechanism in response to suboptimal renal function. Seen from the opposite perspective, PENK could exhibit a direct negative effect on the kidneys through its cardio-depressive effect (138). In **paper III,** the association between PENK and renal function was significantly weaker in the Iraqi group than in the Swedish group which may indicate a protective role for PENK among Iraqis. Increased PENK is associated with lower blood pressure levels. This is presumably due to the stated cardio depressive effect (138). The Iraqi group may need less counter-regulatory production of PENK, considering their lower mean blood pressure or exhibit increased sensitivity towards PENK. This reasoning is of course purely theoretical, and the study cannot infer causality. However, the finding adds to a growing understanding that this ethnic group exhibit mechanisms regarding renal function and blood pressure that differs from the native population in Sweden.

Diabetes

Paper II gives novel information on disproportions in subtypes of diabetes between the two groups. It is most striking that the Iraqi group exhibited pronounced insulin-deficiency in comparison to insulin-resistance. These findings go in-line with previously findings from the MEDIM study, showing that the Iraqi group is exposed to relative insulin deficiency before the development of diabetes (179). Previously defined genetic risk scores of insulin secretion are associated with the most common diabetes subgroups in the Iraqi group; SIDD, MARD and MOD (209), which together with previous data describing a high family burden of type 2 diabetes in the Iraqi group (210) and the GRS findings in this paper – indicate that high risk genetics, contribute more to the diabetes development in the Iraqi group. At the follow-up, the Iraqi group had lower risk for CKD as discussed above. The risk for coronary events was however higher. Previous data on the CVD risk among diabetes

patients in the MEDIM study supports the increased risk in the Iraqi group (13), although the recent longitudinal study showing that diabetes patients from the Middle East exhibited lower cardiovascular mortality should be mentioned (12). This may be interpreted as the Iraqi group being less severely affected if affected by CVD, but the finding needs to be further studied.

Potential mechanisms

There are disparities between the groups regarding characteristics in lifestyle habits. Not surprisingly, the rate of alcohol users was significantly higher in the Swedish born group in all papers (**papers I** and **IV**) that investigated self-reported alcohol use. The relationship between alcohol use and health outcomes are well studied. There is a beneficial relationship between low alcohol consumption and ischaemic heart disease based on observational findings (211). On the other hand, there is a strong correlation between alcohol intake and higher blood pressure with a distinct dose-dependent reduction in blood pressure, if alcohol consumption is reduced, especially if more than two drinks per day (212). The relationship between renal function and alcohol intake is more ambiguous and not that well established. Studies have shown both a protective effect from alcohol on the development of CKD (213), but also association with a faster CKD progression (214). The blood pressure difference registered in **papers I** and **III** and rate of hypertension in **paper II** may thus be partly explained by excessive alcohol consumption in the Swedish-born group, but the potential contributing effect on differences in renal function is more unclear. A potential future research study may be an intervention study aiming at reduction of alcohol intake in this study population. A limitation is that alcohol consumers are defined as those who drink or do not drink in **papers I** and **IV** - regardless of the quantity. As the blood pressure increasing effect is quantity dependent, it would be of interest to further explore quantities in this population.

The papers included in this thesis have not focused or presented differences in dietary intakes between the groups. A sub study within the MEDIM sphere, 'the MEDIM intervention study' included 71 participants from the Iraqi-born group. At baseline, the participants exhibited high fat intake (about 40% of total energy intake). The intake of fibres was below the recommended daily intake (215). The role of diet in relation to hypertension is thoroughly studied although recommendations vary. A recent systematic review on 13 different dietary approaches to blood pressure reduction, suggested the Dietary Approaches to Stop Hypertension (DASH) approach as the most effective (216). This includes a diet rich in fruit, vegetables, whole grains and low-fat dairy with reduction of sodium and saturated as well as total fats (217). The review included a Nordic diet, which could not confirm any reduction in blood pressure although only based on one included trial (218). Dietary intakes in the MEDIM population could be further

studied and especially comparisons between the groups. At first sight from the intervention study, the Iraqi group did not seem to have a beneficial dietary pattern.

Papers I, III and **IV** described ongoing tobacco use with no difference in usage between the groups, hence this factor should not affect the outcome.

Physical activity was described in **paper I**, illustrating that a significant proportion of the Iraqi group was physically active for less than 150 minutes per week. A previous study within MEDIM confirmed that members of the Iraqi group were less physically active by objective measurements by use of accelerometers (219). The Iraqi group also reported more stress in daily life. Low physical activity is recognised as an important risk factor for developing hypertension and several studies have shown manifest reductions in blood pressure, if exercise is augmented (220, 221). It should be noted that there is individual variability in blood pressure response to exercise. Previous family studies have shown significant genetic components to the blood pressure response, but these associations need to be further explored (222). Studies on the exercise-modifying effect on blood pressure have predominantly been studied on Caucasians. The MEDIM intervention study did not show any significant reduction in blood pressure in an Iraqi-born intervention group (n=50) receiving group sessions focusing on healthy diet and increased physical activity (223). This may support that the blood pressure response to exercise is less pronounced in the Iraqi group but needs to be further studied.

Obesity was more prevalent in the Iraqi group in all papers, which contradicts the more favourable renal function and blood pressure profile, considering a solid correlation between higher BMI and higher blood pressure (224) and CKD risk (225). It is, however, noteworthy that the effect of obesity on blood pressure has shown ethnic disparities in repeated studies (226, 227), which may partly be explained by different body compositions depending on ethnicity; hence BMI is a somewhat blunt variable (228). BMI and waist circumference have previously been shown to be less associated to blood pressure in the Iraqi group from the MEDIM population, further suggesting protective properties (15). In a sub-study from the MEDIM on individuals with diabetes, the Iraqi group exhibited a more beneficial lipid profile by metabolite profiling, which may aid in preserving a more favourable blood pressure profile despite more prevalent obesity. This could also suggest disparities in dietary patterns that we are not able to capture, as the same study could not show any difference in dietary intake data (229).

No data are presented on socioeconomic factors in these papers. **Papers I, III** and **IV** are based on a study population, that was included from the Eastern parts of Malmö, which are residential areas more socially vulnerable than the Western parts to reduce socioeconomic bias. Considering the correlation between smoking and low socioeconomic status (230), the similar and higher rate than general of tobacco use could support a successful inclusion in terms of reducing the socioeconomic bias. However, as presented in previous papers on MEDIM, the Iraqi group

exhibited higher rates on unemployment, increased economic insecurity and lower social participation (231) – all features of a lower socioeconomic status. Considering the powerful effect of socioeconomic status on health outcomes (232) – the more favourable blood pressure levels and renal function despite a lower socioeconomic status in the Iraqi group, strengthen the assumption of a true advantage.

As mentioned in the introduction, a "healthy migrant effect" is often seen after migration to a new country (28, 30). In the MEDIM population, the average time spent in Sweden since migration was 16 years among Iraqi women and 17 years among the men (233). It has been shown that the healthy migrant effect often diminishes after time (234) and it is also acknowledged that there is a considerable difference in the magnitude of the healthy migrant effect depending on the country, especially studied in the Europe (235). The confounding influence from the "healthy migrant effect" on the results in this thesis is thus ambiguous. The considerable time since migration applicable for the study populations in **papers I, III** and **IV** argues against a profound influence.

As described previously, studies on second-generation versus first-generation immigrants are sparse; a Swedish register study showed mortality advantages in first generation immigrations, which dissolved in the second generation (12) arguing for a potentially strong effect from acculturation. It would be of great interest to study renal function and blood pressure in a similar fashion as in thesis in a second-generation immigrant population, aiming at investigating whether the proposed protective attributes remain.

If going further to other theoretical domains - early life factors are receiving increased attention, also in the context of cardiovascular diseases and its risk factors. The relationship between low birthweight (LBW) and future risk for high blood pressure as well as increased CVD risk is well established (236, 237). The potential effect on renal function has been illustrated by the association between LBW and a reduced number of nephrons leading to reduced eGFR (238, 239) The potential contributing role of ethnicity to the relationship between LBW and health outcome, has been studied in relation to blood pressure in the US, concluding that the relationship between low birthweight and increased blood pressure may be more pronounced among African Americans, than among Caucasians (240). Existing information on birthweights in Iraq in specific are sparse. A 2019 report from UNICEF/WHO estimated the LBW (as defined as less than 2500g at birth) prevalence at 11.3% in Middle East/North Africa as compared to 6.9% in Western Europe. A high proportion (36.1%) of all births lacking information on birthweight in the Middle East/North Africa group, however illustrates the unreliability of the data (241). To gather birthweight statistics from the Iraqi immigrant population in the MEDIM-study should be fairly difficult but it is clearly a topic of future interest.

Adaption to the environment is an important factor in evolutionary development. Today's variations in disease risk and prevalence may be partially explained by our human history starting with *homo sapiens* and the migration out of Africa around 60,000 years ago exposing our ancestors to different environmental challenges. The environmental selection during historical time is today evident in the human genome (242).

The most striking environmental difference between Iraq and Sweden is the climate with Iraq being substantially warmer and drier. Around 90% of Iraq's annual precipitation (rain) is occurring in the winter between November to April. In the central/southern parts of Iraq, precipitation could be as low as 100 mm/year (243, 244) which could be compared to around 600 mm/year, more evenly distributed throughout the year in Sweden (245). Surviving in very hot climate is believed to favour adaptions of renal function including the bodily homeostasis of water and sodium handling to avoid dehydration and sodium loss. This has been studied in other mammals.

During recent decades, theories on disposition to obesity have evolved adjacent to new findings on variations in basal metabolism. Thermogenesis in brown adipose tissue could be enhanced in populations with ancestral exposure to a cold climate, which raises the basal metabolism rendering higher resting metabolic rate, lowering obesity risk (246, 247). One could thus hypothesise that the Iraqi group is more prone to obesity and sensitive to a sedentary lifestyle, partly explained by their ancestry and climate-driven evolution. This, however, contradicts the fact that the Iraqi group have a more favourable blood pressure profile and renal function - and additionally speaks for obesity being a weaker cardiovascular risk factor in this group.

To further investigate the role of evolutionary adaption, studies in other mammals can provide insights. Dromedaries (Africa and the Middle East) and Camels (Inner Asia) have adapted to extreme environments being tolerant to water losses of around 25% of the total body weight and temperatures over 40 C° (248). This is intriguing from a renal standpoint. A genomic analysis on camels, dromedaries and alpacas from 2014 identified key genes related to desert adaptions, with camels exhibiting unique genomic properties indicating a more efficient salt metabolism and transport. Also, genes involved in the sodium reabsorption in the kidneys were upregulated in camels during water restriction indicating that camels might be able to regulate sodium reabsorption depending on water supply. Further, it was also shown that camels, known for exhibiting high blood glucose levels (249) that could be a factor to support in osmoregulation and water reabsorption (250). Altogether, these findings indicate that camels exhibit evolutionary adaptions of renal function to a warm and dry climate, which may have implications also in human physiology. It is tempting to hypothesise that people from Iraq may possess evolutionary advantages related to renal function that may at least partly explain findings in this thesis.

This further increases the great interest in salt sensitivity, as this interferes with the mechanisms above. As described in the Introduction, there exits variability in salt sensitivity between populations. Hence it would be of great interest to study potential differences between the MEDIM study groups in this respect to either prove or reject the hypothesis of an evolutionary advantage in salt-handling for people with an ancestry shaped by very hot and dry climate zones like deserts.

Methodological considerations

Some of the limitations has been reviewed throughout the Discussion part. Considering the methodology, the thesis is based on three different studies, which adds strength, enabling comparisons. All studies use the same laboratory methods for determining creatinine and cystatin C, reducing analytical bias.

Papers I and **III** are based on a cross-sectional study with the major disadvantage – the inability to infer causality. Both of these papers are designed in a similar fashion with estimation renal function in focus. The matter of renal function estimation is thoroughly discussed above. In **paper I**, with a previous history of CVD were excluded (6.2% in the Iraqi group and 8.4% in the Swedish group). This was not the case in **paper III** which may be seen as inconsistent. The objective was however not to compare these papers and they should be viewed as separate contributions with different foci. The proportion of men was higher in the Iraqi group in all papers. Comparisons were however adjusted for sex. Both blood pressure levels and renal function are more favourable among women in the material, hence, the male dominance among Iraqis should not affect the primary outcomes, rather the opposite. Due to laboratory shortcomings, some of the participants were excluded. As basic characteristics of the missing group were close to similar to the people examined, this should not amount to a selection bias. As mentioned previously, the lack of albuminuria as a study variable is a limitation.

Paper II is based on the ANDIS study (177). It includes a follow-up part which strengthens the findings of this thesis with regard to renal function. The duration of the follow-up can be considered as relatively long which brings a strength to the study. The study however lacks data from baseline on lifestyle habits, socioeconomic background and blood pressure profiles which is a clear limitation. Potential confounding factors related to the difference in diabetes complications are thus untold. The smaller study sample born in Iraq renders uncertainties, especially for the follow-up analyses. To increase the statistical power, one future option may be to expand the study population with participants born in other countries in the Middle East. The difficulties in GFR estimation are discussed above.

Paper IV suffers from the small study sample, due to the unforeseen early termination because of the COVID-19 pandemic. It should be a priority to restart the study with the addition of new participants in the future. Thus, the results are

statistically uncertain and should be viewed as preliminary only. The study used well-established methods like c-f PWV and iohexol clearance, which is a strength. The investigations carried out during the main study day were standardised and followed a specific outline. Only three research nurses performed the investigations and only one physician (CN) examined the participants prior to the main study day, decreasing the risk for personal errors and promoting continuity. The investigations during the main study day used different time slots throughout the day. This might interfere with the results as some analyses, such as the measurement of renal function vary throughout the day. The inclusion of participants was difficult, primarily caused by the fact that the study design involved two physical visits, one of which took around five hours and a blood sampling in between the visits. As the visits took place during working days, this may amount to a selection bias. To improve recruitment, the study added 23 participants from outside the original MEDIM study population, of which 13 followed through the whole study. These participants consisted of relatives and friends of the original participants who volunteered. This might amount to a selection bias as these participants could have various personal reasons for their volunteering such as a wish for a "free" health exam and so on. The main reason for the extra inclusion was to logistically optimise the study flow and effectiveness as these participants could fill empty time slots. In future analyses, original participants and "extra" participants could be separated, especially for future follow-up analyses based on the original MEDIM study. The study intentionally aimed to include a "healthy" population to study mGFR among subjects with normal renal function. With a low number of participants, having varying GFR levels would render even lower statistical power, hence the first objective was to study a population representing normal renal function. In the future, subgroups could be included with various stages of CKD as it would be of interest to study the accuracy of eGFR estimation in such subgroups as well.

Conclusion

- Iraqi-born immigrants in Sweden have a more favourable renal function than a controls from a native Swedish-born population as denoted by three different cohorts. Additionally, the risk of developing chronic kidney disease was lower among subjects with diabetes in the Iraqi-born group during a follow up period.
- The association between blood pressure levels and renal function is weaker among Iraqi-born immigrants which could indicate a protective mechanism from the negative influence of blood pressure on renal function in this group.
- Diabetes-related traits differ between Iraqi-born immigrants and native Swedes. In particular, Iraqis were more insulin-deficient but less insulin-resistant than the Swedes. The risk for diabetes complications also differs.
- Pro-Enkephalin (PENK), a biomarker proposed to exhibit a protective direct effect on the kidneys, is more weakly associated with renal function among Iraqi-born immigrants. This may be part of a protective mechanism in this group to preserve a better renal function.
- There are suggestive inconsistencies in eGFR estimation among Iraqi-born immigrants depending on choice of equation that should be further studied. This was especially true for the CAPA equation which was significantly more inaccurate in the Iraqi-born group.
- Iraqi-born immigrants seem to be protected against CVD in previous studies. This protection against CVD may partly be due to differences in the regulation of blood pressure and renal function. Further mechanisms and causality aspects should be explored. It is intriguing to hypothesize on an evolutionary advantage shaped by an ancestry from a very warm and dry climate when preservation of water and electrolytes are essential for survival, thus implying the need of more robust and flexible renal function.

Future perspectives

This thesis is, in a way, only scratching the tip of an iceberg. There is still much to explore, and my hope is that this work elucidates potential and provides inspiration for future research in this field. In the following section, I will continue on from the discussion to give some concrete examples of what I believe would be of significant interest to study in the future.

A salt sensitivity-study on these populations would be novel and of greatest interest, hence it would aid in the understanding of potential protective mechanisms and could strengthen/contradict the assumption of climate-induced renal protection in the Iraqi born group. This would preferably be done by use of a dietary protocol (251) and should be implementable by inviting a portion of the original MEDIM study population.

A longitudinal follow-up study on the MEDIM study population has in some ways already begun with the MEDIM 2019 study. With an increased number of participants, follow-up information would provide information on the development of renal function, blood pressure and other cardiovascular risk factors over time. It would also help in understanding the extent of a possible "healthy migrant effect" in the Iraqi group as it would study health disparities after a long-term residency in Sweden.

A study on the 'Shrunken poor syndrome' (SPS) and whether it is affected by ethnicity as a potential renal protecting mechanism is another mechanism. SPS has gained increased attention recent years. It is defined as $eGFR_{cystatin\ C}$ being less than 70% of $eGFR_{creatinine}$, which has been shown to be associated with worse general outcomes (252). SPS could easily be investigated in the MEDIM cohort with existing data.

A MEDIM Offspring Study could be another future project. As outlined above, the health of second-generation immigrants often tend to resemble the health of the native population. A study inviting the offspring from the original MEDIM study participants could bring valuable information on this as well as contributing to the mapping of family patterns behind these diseases. A second option is to create an entirely new cohort including second-generation immigrants with parents born in Iraq and compared to a control group.

The possibility of genetic studies. With increasing knowledge of SNPs associated with common diseases, the potential of GWAS analyses has emerged. Based on today's knowledge it would be possible to perform GWAS analyses in relation to blood pressure regulation, renal function and salt sensitivity as crucial mechanisms. As blood samples are stored from the original MEDIM study in a biobank, this would be rather uncomplicated to achieve.

Populärvetenskaplig sammanfattning på svenska (Summary in Swedish)

Den vanligaste dödsorsaken såväl globalt som i Sverige utgörs av hjärt-kärlsjukdomar. Det finns ett flertal faktorer som ökar risken att drabbas av dessa sjukdomar, däribland högt blodtryck, diabetes samt nedsatt njurfunktion. Dessa riskfaktorer är även starkt sammankopplade där exempelvis både högt blodtryck och diabetes är riskfaktorer för försämrad njurfunktion. På så vis ingår dessa riskfaktorer i ett intrikat samverkande system. Vi vet idag en hel del kring hur vi ska hantera dessa riskfaktorer men vi har fortfarande oerhört mycket att lära, i synnerhet angående skillnader mellan befolkningsgrupper.

Under de senaste årtiondena har vi sett en tilltagande globalisering och ökandes migrationsströmmar. I synnerhet har västerländska länder, däribland Sverige sett en stigande andel invandring från Mellanöstern. Det är vida känt att risken för att drabbas av typ 2 diabetes är ökad i befolkningar från länder i Mellanöstern. Med tanke på att en allt större del av Sveriges befolkning härstammar från dessa länder, har detta gett upphov till ett behov av vidare forskning inom dessa grupper för att på sikt kunna upprätthålla en jämlik hälso- och sjukvård.

Ett led i denna ambition var starten av den Malmöbaserade befolkningsstudien MEDIM (betydelsen av Migration och Etnicitet för Diabetesutvecklingen I Malmö) som genomfördes mellan åren 2010–2012. Studien inbegrep Malmöbor födda i Irak samt Malmöbor födda i Sverige som kontrollgrupp. Studien kunde visa att typ 2 diabetes var nästan dubbelt så vanligt förekommande bland individer födda i Irak. Vidare sågs även att den irakfödda gruppen i större utsträckning var drabbad av övervikt, högre blodfettsnivåer samt rapporterade mindre fysisk aktivitet i jämförelse med den svenskfödda gruppen. Detta är även riskfaktorer som inte bara ökar risken för diabetes men även risken för högt blodtryck, försämrad njurfunktion och i slutändan för hjärt-kärlsjukdomar. Trots detta sågs i MEDIM studien att blodtrycksnivåerna bland irakfödda faktiskt var lägre, vilket är något av en paradox. Vidare har det i andra studier även framkommit se att risken för hjärt-kärlsjukdomar faktiskt är lägre bland invandrare från Mellanöstern, vilket skulle kunna tyda på att denna befolkningsgrupp uppvisar skyddande faktorer som vore av stort intresse att närmare studera.

Avhandlingens syfte var således att kartlägga viktiga riskfaktorer för hjärt-kärlsjukdom, i synnerhet högt blodtryck, nedsatt njurfunktion samt diabetes hos invandrare från Mellanöstern för att värdera huruvida det finns tecken på skyddande faktorer inom denna grupp, vilket i framtiden skulle kunna bidra till förbättrad prevention av hjärt-kärlsjukdomar.

I delarbete I undersöktes blodtryck och njurfunktionen hos cirka 1200 irakfödda Malmöbor och 650 svenskfödda Malmöbor. Resultaten visade att den irakfödda gruppen både hade lägre blodtrycksnivåer samt bättre njurfunktionsnivå. Det gick även att se att njurfunktionen inte var lika starkt beroende av blodtrycket bland irakfödda. Vanligtvis ses ett tydligt samband mellan stigande blodtryck och avtagande njurfunktion. Njurarna är genom flera mekanismer även starkt involverade i blodtrycksregleringen. Resultaten skulle kunna tala för att invandrare från Mellanöstern är relativt sett skyddade mot försämrad njurfunktion genom lägre blodtryck i förhållande till kroppsmått (övervikt/fetma) och en svagare påverkan från blodtryck på njurfunktionen.

I delarbete II undersöktes diabetes och dess komplikationer bland cirka 200 irakfödda Skånebor samt 7500 svenskfödda invånare i Skåne. Dessa resultat är baserade på data från den pågående ANDIS (Alla Nya Diabetiker i Skåne) studien som inkluderar diabetespatienter i Skåne vilka nyligen fått sin diagnos. Dessa följs sedan under flera år utifrån sjukhusregister för att bedöma förekomst av vanliga komplikationer till diabetes, såsom njursvikt, stroke, etc. Studiens data har tidigare legat till grund för ett förslag om att diabetes bör indelas i fem olika grupper i stället för de två traditionella, då utmärkande diabetesdrag skiljer sig ganska markant åt mellan drabbade individer, medförandes olika risk att drabbas av komplikationer.

Resultaten visade att den irakfödda gruppen hade en större andel individer med diabetes som hade tydlig insulinbrist i stället för insulinresistens. En större andel av irakfödda hade även en mildare variant som är kopplad till övervikt men som sällan ger upphov till allvarliga komplikationer. Vid uppföljningen sågs det att risken att drabbas av njursvikt var lägre bland irakfödda medan risken för hjärtinfarkt var större.

I delarbete III studerades en ny biomarkör som är kopplad till njurfunktion och även anses ha en direkt påverkan på njurarna. Markören heter Pro-Enkephalin och är en sorts opiod, en typ av substans som finns naturligt i kroppen. Tidigare har det kunnat ses att högre nivåer av Pro-Enkephalin är kopplat till försämrad njurfunktion. Nivåerna av Pro-Enkephalin i blodet och dess koppling till njurfunktion studerades hos cirka 1250 irakfödda Malmöbor samt 700 svenskfödda Malmöbor. Resultaten visade att nivåerna av Pro-Enkephalin inte skiljde sig åt trots att njurfunktionen var bättre bland irakfödda. Vidare sågs en svagare koppling mellan Pro-Enkephalin och njurfunktion bland irakfödda vilket skulle kunna tala för att Pro-Enkephalin är involverat i att upprätthålla en bättre njurfunktion bland irakfödda.

I bestämningen av njurfunktionen finns det vissa svårigheter. I sjukvården uppskattas vanligen njurfunktionen utifrån blodmarkörer, vanligen kreatinin eller cystatin C. Utifrån dessa värden kan njurfunktionen uppskattas (estimeras) via olika formler, så kallat eGFR, d.v.s., hur mycket blod som njurarna filtrerar varje minut. Det finns dock nackdelar med dessa labmetoder eftersom de bland annat påverkas av kost, fysisk aktivitet, inflammation, med mera Det har även visat sig att de formler vi använder oss av kliniskt skiljer sig åt gällande tillförlitlighet. Formlerna har även visat sig ha olika tillförlitlighet beroende på etnisk härkomst. Den mer exakta metoden för att mäta njurfunktion är att tillföra ett ämne till kroppen som skall utsöndras via njurarna för att sedan kunna mäta koncentrationen av detta ämne vilket ger en mer tillförlitlig uppskattning av njurfunktionen. Detta kan bland annat åstadkommas genom att tillföra röntgenkontrastmedlet iohexol. I delarbetena I, II samt III användes flertalet olika formler för att beräkna njurfunktion. Det fanns en osäkerhet i hur korrekta dessa var, i synnerhet inom den Irakfödda gruppen då tillförlitligheten av dessa formler för njurfunktion är outforskade i nämnd befolkning.

I delarbete IV studerades därför njurfunktionen med den mer exakta metoden iohexolbelastning bland 29 irakfödda Malmöbor och 31 svenskfödda Malmöbor. Det visade sig att det fanns tecken till att de vanliga formlerna för njurfunktionen möjligen fungerar något sämre bland Irakfödda. Dessvärre blev deltagarantalet lågt på grund av covidpandemin och det är därför svårt att för närvarande dra säkra slutsatser. I undersökningen undersöktes även deltagarnas artärstelhet som är kopplat både till blodtrycksnivå och risk för hjärt-kärlsjukdom. I det begränsade materialet fanns ingen skillnad i uppmätt artärstelhet mellan grupperna.

Sammantaget visar avhandlingen att det finns tecken på skyddande faktorer bland irakfödda personer där njurfunktionen genomsnittligt är bättre än hos svenskfödda, vilket kan bero på en mer gynnsam inverkan från lägre blodtryck. Diabetes tar sig även annorlunda uttryck bland irakfödda där man snarast har diabetestyper som är mer gynnsamma mot njurfunktionsförsämring. Man kan spekulera i att dessa mekanismer kan bidra till att skydda irakfödda mot hjärt-kärlsjukdom. En intressant teori är att härstamning från ett varmare klimat kan ha bidragit till en evolutionsmässig tendens till ”starkare” njurar för att kunna överleva torka med vätskebrist och noggrann reglering via njuren av salt- och vatten-balans.

Det ska tilläggas att i befolkningsstudier likt dessa är det inte möjligt att bevisa äkta samband, även benämnt kausalitet. Det går inte att helt uttala sig om statistiska samband – exempelvis huruvida kopplingen mellan njurfunktion och blodtryck skulle vara en del av ett äkta orsakssamband eller om det påverkas av andra bakgrundsfaktorer. Därmed bör resultaten i första hand ses som indicier och hypotesgenererande samt förhoppningsvis inspirerande till framtida forskning.

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