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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Title: Aspects of insulin secretion and action in Middle Eastern immigrants to Sweden

Background: Middle Eastern (ME) immigrants to Europe have a higher prevalence of type 2 diabetes (T2D) as compared to Europeans. Previous findings from the MEDIM population-based cohort (Impact of ethnicity and migration on diabetes in Malmö) have shown that ME immigrants are more insulin resistant before developing T2D as compared to native Swedes. However, knowledge is still lacking if there are differences across ethnicities on how insulin secretion and action change with increasing age. Furthermore, T2D is linked to an increased incidence of cancer, cardiovascular disease (CVD), and all-cause mortality (ACM) but differences in incidence rates across ethnicities remain unknown. Vitamin D deficiency is linked to metabolic disturbances, but knowledge concerning differences in the associations between vitamin D (25(OH)D) and glucose regulation across ME and European ethnicities is still unknown.

Aims: In the MEDIM cohort: 1) study changes in insulin action (assessed by insulin sensitivity index (ISI)) and secretion (assessed by oral disposition index (DIo)), with increasing age, and the potential impact of ethnicity, 2) In an 8-year register based follow up of the MEDIM cohort, study ethnic differences in the incidence of ACM, cancer- and CVD, as well as case-specific mortality (CSM). 3) Study differences across ethnicities in the levels of 25(OH)D and PTH, and if differences in glucose regulation are explained by 25(OH)D and PTH. In the MEDIM culturally adapted randomized controlled trial (RCT): 4) to study the effect of lifestyle intervention in ME immigrants on the levels of 25(OH)D, insulin-like growth factor 1 (IGF-1), Pro-neurotensin (Pro-NT) and adiponectin, and whether the effect of the intervention on ISI and DIo is mediated by these hormones.

Methods: Residents of Malmö, born in Iraq or Sweden aged 30-75 years old, were invited to participate in the MEDIM study between 2010-2012. Oral glucose tolerance tests were performed (0,30,60,120 min) to calculate ISI and DIo using the Matsuda formula. In paper I, we studied changes in ISI and DIo with increasing age. Associations were studied using multiple linear regression analysis. In paper II, we conducted an 8 year follow-up where register data were retrieved from baseline until the 31st of December 2018 to assess the adjusted hazard ratios (HR) for the relationships between ethnicity, ACM, cancer, CVD events and CSM. In paper III, in the MEDIM cohort, multiple regression analysis was assessed to study the potential associations between 25(OH)D, ISI and DIo across ethnicities. In paper IV, Iraqi immigrants at high risk of T2D were invited to participate in the MEDIM culturally adapted intervention RCT. We used mixed model regression analysis to study whether the effect of the intervention was mediated by the changes in the levels of IGF-1, 25(OH)D, Pro-NT or adiponectin.

Results: Our data show that 1) ISI and DIo decreased with increasing age regardless of ethnicity with the Iraqis having lower ISI in all age groups 2) The adjusted ACM, cancer, CVD and CSM rates were lower among Iraqi immigrants compared to native Swedes. 3) The levels of 25(OH)D were significantly lower and the levels of PTH were higher among Iraqi immigrants compared to native Swedes. The lower levels of ISI in Iraqis compared to Swedes were explained by differences in 25(OH)D. 4) The effects of lifestyle intervention on ISI and DIo were associated with changes in the levels of 25(OH)D.

Conclusion: This thesis shows a high risk of earlier diabetes onset in Iraqi immigrants as reflected by lower insulin sensitivity in corresponding age categories and worse glucose regulation over time.

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To my father, Fadhel Dhaher Mahdi

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Abbreviations

ACM	All-cause mortality
BMI	Body mass index
CDR	Cause of Death Register
CIO	Corrected insulin response
CSM	Case-Specific Mortality
CVD	Cardiovascular disease
DIo	Oral disposition index
f-glc	Fasting glucose
GH	Growth hormone
GLP-1	Glucose-like peptide 1
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems 10th revision
IDF	International Diabetes Federation
IGF-1	Insulin-like growth factor 1
ISI	Insulin sensitivity index
LDL	Low-density lipoprotein
MEDIM	The impact of Migration and Ethnicity on Diabetes In Malmö
ME	Middle East
MENA	Middle East and North Africa
MET	Metabolic Equivalent of Task
NDR	National Diabetes Register
NPR	National Patient Register
NT	Neurotensin
NTR	Neurotensin receptor
Pro-NT	Pro-neurotensin

PTH	Parathyroid hormone
RCT	Randomly Controlled Trial
T2D	Type 2 diabetes
VDR	Vitamin D receptor
25(OH)D	Vitamin D

Original papers

The thesis is based on the following papers:

I. Dhaher, N.F., et al., Insulin secretion and action with increasing age - A comparison between Middle Eastern immigrants and native Swedes. Heliyon, 2022. **8** (10): p. e10913.

II. Dhaher, N.F., et al., Cancer, cardiovascular disease, and all-cause mortality in Iraqi- and Swedish-born individuals in Sweden: the MEDIM cohort study. Sci Rep, 2023. **13** (1): p. 6129.

III. Dhaher, N.F., et al., Glucose regulation and association with Vitamin D and parathyroid hormone – differences across Middle Eastern and Caucasian ethnicities. Journal of Diabetes & Metabolic Disorders, 2025.

IV. Dhaher, N.F., et al., Impact of lifestyle intervention on vitamin D, Adiponectin, Insulin-like growth factor 1 and Proneurotensin in overweight individuals from the Middle East. Primary Care Diabetes, 2024.

Prologue

I entered the research process with humble research experiences, mainly gained from the mandatory scientific project within internal medicine board. All I had with me when first meeting Louise Bennet, who came to be my main supervisor, was a genuine interest and a belief that research is rather an obligation than an option if I am to consider myself as a fully equipped MD. Having an Iraqi origin and connections with the Iraqi community in Malmö, I came to know about the MEDIM study. At that time, I was working at a primary care unit close to the area of Rosengård, where the MEDIM participants were recruited, and I thought of the great benefit the study would contribute to the Middle Eastern immigrant group in Sweden. Nine years later I was introduced to Louise Bennet when expressing my interest in diabetes research. Louise embraced my enthusiasm and has ever since been my guide through the process giving me the tools to proceed but with a high level of independence and trust. I had the benefit of working with the MEDIM cohort with participants already recruited and a fully equipped data bank to be explored.

My focus at the beginning of the research process was to apply for the mandatory courses with the purpose of getting proper education and introduction, also to meet other research fellows and exchange experiences. My residency in diabetology and endocrinology enhanced my research and vice versa. Not only having the benefit of working together with diabetes patients, and diabetologists, I also was given the opportunity to participate in different educational activities related to diabetes and diabetes research.

During the Covid 19 pandemic, the priorities became different but with the support of the supervisors and co-authors the project kept progressing and all the papers produced are a result of hard teamwork and intensive communication. Developing towards autonomy as a scientist is an ongoing process and even if this thesis is now put into covers, the journey of learning proceeds with more to learn and discover as well as challenges to overcome.

Background

Global, regional and national burden of Type 2 diabetes

Diabetes in Middle East and North Africa

Type 2 diabetes (T2D) is a serious, chronic disease and represents the eighth leading cause of disability and death combined worldwide [1]. The Global Burden of Disease Study from 2021, estimates that over half a billion (529 million, 6.1%) people of all ages, or 485 million adults have diabetes, with the majority 96% suffering from T2D. This indicates that by 2050 more than 1.3 billion people could be living with diabetes, which gives diabetes pandemic proportions [1]. At a super-regional level, the highest age-standardised total diabetes prevalence of 9.3% is in the North Africa and Middle East (MENA) region with 11 countries having country-specific rates of more the 10% [2]. Iraq has the highest country-specific, age-standardised total diabetes prevalence in the MENA region with a prevalence rate of 15.3%, whilst nationally, Qatar has the world's highest age-specific prevalence of diabetes at 76.1% in the ages 75-79 years [2]. The global age-standardised prevalence of diabetes increased by 90.5% between 1990 and 2021, with the highest increase in diabetes prevalence exceeding 100% in the MENA region (161.5%). A rise of 82.7% in the projected increase in total age-standardised prevalence of diabetes is expected by 2050 in this region [2].

Sweden

According to the National Diabetes Register (NDR) statistics from 2023, there are approximately 439 760 individuals (>18 years) currently suffering from T2D in Sweden, i.e. a prevalence of approximately 4.2% [3]. Between 2007 and 2013 the incidence of diabetes in Sweden remained constant (4.4% per 1000) but with constant incidence and increase in relative survival the prevalence is expected to increase and reach about 10% by 2050 [4].

Risk Factors

In a systematic analysis for The Global Burden of Disease Study from 2021 [2], high body mass index (BMI) was shown to be the primary risk factor for T2D worldwide [2]. Genetic susceptibility in combination with a wide variety of lifestyle factors are also of great importance to the development of T2D, such as sedentary lifestyle, smoking and alcohol consumption [5]. A number of other risk factors account for the uncontrolled rise of T2D in the MENA region, such as rapid urbanisation, changes in dietary habits, multiple pregnancies and lack of health education [6]. In the Arabic world, there is also increasing evidence about possible genetic risk factors behind the alarming increase in T2D prevalence [7].

A significant risk factor for developing T2D and obesity is migration, which includes migrating from the native country to another country or within the same country from one habitat to another or rural to urban. Urbanisation and westernisation often lead to the availability and abundance of calorie-rich, low-fibre foods as well as sedentary lifestyles [8]. Urbanisation of rural areas carries many advantages in terms of access to improved medical services and education but creates significant differences in the rate of T2D [6]. In a study from Saudi Arabia, the prevalence of T2D was 12% in males and 14% in females in urban communities versus 7% and 7.7% in rural areas [9]. Similar findings were reported from Oman and North Africa [10, 11]. In studies from Basrah in Iraq, the prevalence of T2D was 7.4% in rural areas and 19.7% in urban areas [12, 13]. The higher T2D prevalence in urban than rural areas of low- and middle-income countries may be explained by better access to health services in urban areas resulting in proper diagnosis, a less active lifestyle and access to high-calorie food [14-16]. In high-income countries, physical inactivity and obesity rather than urbanisation are the main determinants of T2D prevalence [14].

Data from the United Food and Agriculture Organization from 2010 was used to estimate the dietary intake of 20 countries in the MENA region in a comparative risk assessment analysis [17]. The analysis showed suboptimal intake of protective diets, fruits vegetables and seafood, in combination with greater consumption of harmful diets, processed meat and trans fatty acids [17]. Sedentary lifestyles are widespread in the MENA region due to cultural barriers regarding women's physical activity and global warming with high temperatures for longer periods discouraging people from outdoor activities. The overall prevalence of physically active adolescents in the Eastern Mediterranean countries is estimated to be 19%, the highest in Oman (26%) and the lowest in Egypt (9%) [18]. As a comparison, survey data sponsored by the European commission from member countries in 2022 showed that nearly four in 10 Europeans say they exercise or play sport at least once a week [19].

Migration and health

Over the past five decades, the estimated number of international migrants has been increasing and in 2020 a total of 281 million people were estimated to be living in countries other than their country of origin [20]. Political instability, war, persecution and climate changes in the MENA region have forced millions of people to leave their home countries and seek a more stable future in Northern Europe [21]. Sweden has adopted an open-door policy on immigration, offering healthcare, education and employment opportunities to immigrants. Furthermore, Sweden is one of the European countries with the highest reception of refugees per capita. Since the early 2000s, Sweden has received over a million immigrants. Currently, about 20% of the total population of around 10 million inhabitants is born outside Sweden. If persons born in Sweden to both parents, who were born outside of Sweden are included, the percentage reaches 27% [22]. ME immigrants constitute the largest group of non-European immigrants to Sweden. The city of Malmö has the highest proportion of inhabitants born outside of Sweden comprising 35.9% of the population, with the largest immigrant groups originating from the ME [22].

The prevalence of T2D among non-European immigrants to Sweden is 2-3 times higher as compared to the prevalence in native-born Swedes, particularly among ME immigrants [23-26]. Overweight and obesity are the primary risk factors for T2D among immigrant groups to Sweden [24, 25]. Other risk factors associated with the increased risk of T2D observed in immigrant groups are sedentary lifestyle, family history of diabetes, and socioeconomic factors such as low education unemployment and failure to acculturate to the new society in the host country [27-29]. Nutrition transition and dietary acculturation are two driving forces of change in lifestyle and consequent health outcomes in immigrant groups to high-income countries, shifting from traditional food to ultra-processed, and energy-dense food with subsequent overweight and obesity [30].

Non-Western immigrant groups in Western countries exhibit lower levels of physical activity compared to natives, with a number of contributing factors related to cultural, religious and environmental barriers as well as socioeconomic challenges [31]. The fact that ME immigrants originate from countries with the highest T2D prevalence worldwide and their risk is potentiated by the urbanisation and westernisation processes, makes them a relevant group to study with regard to T2D risk.

The MEDIM Study

With the purpose of comparing and determining the prevalence of T2D and the frequency of intermediate risk factors in ME immigrants to Sweden the MEDIM study (the impact of Migration and Ethnicity on Diabetes in Malmö), a cross-

sectional population study, was conducted between 2010 and 2012 in Malmö [29]. Residents of Malmö, born in Iraq or Sweden, 30-75 years old were randomly selected from the census register and invited to participate in the study.

MEDIM provided a comparison of the prevalence of T2D, and diabetes-related risk factors of Iraqi-born residents in comparison to native Swedes. All participants were provided oral and written informed consent and signed the informed consent form prior to participation. The participants provided self-reported information regarding lifestyle and dietary habits as well as information regarding family history of diabetes and their medical history. It was mandatory to bring an updated list of current medications. The information and communication with the participants were provided in their native language (Swedish or Arabic). Trained research nurses conducted the health examinations of the participants as well as oral glucose tolerant tests (OGTT) with blood test analysis.

Data from over 2000 participants has enabled a better understanding of the mechanisms underlying the increased risk of T2D as well as awareness of this high-risk group [29]. The results from the MEDIM study showed that the prevalence of T2D was twice as high (11.6% vs. 5.8%) among Iraqi-born immigrants compared to native Swedes. Iraqi ethnicity was identified as an independent risk factor for T2D, diabetes-related risk factors such as obesity, physical inactivity and a positive family history of diabetes were all more prevalent in the Iraq born group [29]. Insulin sensitivity was shown to be lower in the Iraqi group even in normoglycemic subjects with normal BMI and waist circumference, thus revealing a different risk factor profile among Iraqis [29]. Impaired insulin action contributed to a greater extent to the risk of T2D in the Iraqi population. Insulin secretion, corrected to the level of insulin resistance was generally lower among the Iraqis revealing a decline in the function of the β-cells even in subjects free from T2D [29]. Table 1 shows the characteristics of the Iraqi-born participants compared to the Swedish control group.

Table 1:
Characteristics of the MEDIM study participants.

Variable	Country of Birth		
	Iraq (n=1398)	Sweden (n=757)	P-value
Age (years)	46.2 (9.6)	49.5 (11.2)	<0.001
Male sex, n (%)	818 (58.5)	400 (52.8)	0.012
Body mass index, kg/m^2	29.3 (4.5)	27.3 (4.7)	<0.001
Waist circumference (cm)	96.7 (11.2)	93.8 (13.5)	<0.001
Minutes physically active/week	114 (125)	238 (147)	<0.001
HbA1C (mmol/mol)	37.9 (10.0)	36.3 (8.1)	<0.001
Fasting glucose (mmol/L)	5.9 (1.5)	5.7 (1.2)	<0.001
Smokers, n (%)	285 (23.9)	175 (25.4)	0.410
Alcohol	239 (17.9)	606 (81.1)	<0.001
Family history of diabetes, n (%)	587 (49.2)	186 (27.0)	<0.001
T2D, n (%)	11.6 (162)	5.8 (44)	<0.001

Crude data are presented as means (SD) or as numbers (percentages). Family history refers to biological parents, children and/or siblings.

Insulin action and secretion, ethnic differences

T2D is a polygenic disorder with genetic variants interacting with environmental factors leading to the development of the disease [29]. Defective insulin secretion by pancreatic β-cells, and impaired insulin sensitivity are the main pathophysiological defects in T2D [29]. Glucose homeostasis is maintained by the simultaneous functions of the β-cells, the liver and the peripheral tissues (primarily muscle tissue) [29]. The aetiology of T2D is described in stages with impairments in the glucose homeostasis beginning almost a decade prior to disease development, the first stage being a compensatory period when insulin secretion increases to compensate for insulin resistance to keep the glucose levels stable, this is followed by a decrease in the β-cell function and finally an unstable period with rapid rise in glucose to an overt T2D disease [29]. Ethnic differences regarding insulin sensitivity and secretion have been reported in populations which have not yet developed diabetes [32, 33] and different mechanisms seem to contribute to diabetes development in different ethnic populations. In the MEDIM cohort, Iraqi individuals free from T2D were reported to be more insulin resistant compared to Swedish-born participants [32]. In populations of ME and Asian ethnicity, insulin-deficient diabetes is reported to be more prevalent whereas in African populations insulin resistant diabetes is more common than in European populations [34-37]. Data from the ANDIS cohort showed that severe insulin-deficient diabetes was almost twice as common among the Iraq-born group compared to the Swedish-born control group, whereas severe insulin-resistant diabetes was less prevalent [37].

Figure 1 shows insulin secretion (CIR) in relation to insulin sensitivity index (ISI) in participants without diabetes born in Iraq or Sweden from the MEDIM cohort.

Ageing is a process associated with alternations in glucose metabolism, this includes both insulin resistance and beta cell dysfunction [38]. Glucose tolerance progressively declines with increasing age, leading to a higher prevalence of T2D and post prandial hyperglycaemia [39]. Another fact making T2D more prevalent in the elderly population is the decrease of β-cell sensitivity to incretin hormones [39]. Little is known about the progression of insulin secretion and action over time across different populations.

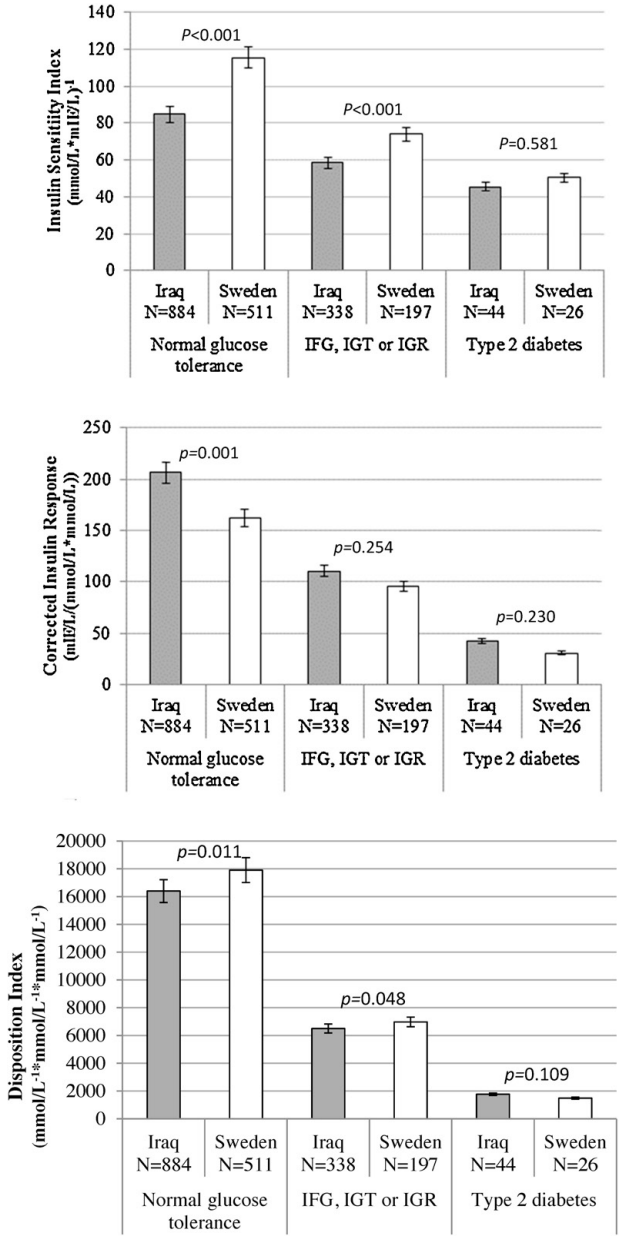

Figure 1 from the MEDIM cohort by Bennet et al [32], shows insulin secretion (CIR), in relation to insulin sensitivity index (ISI) in participants without diabetes born in Iraq or Sweden.

Ethnicity, all-cause mortality and case-specific mortality

Several studies from Europe and North America have reported lower mortality rates among first-generation immigrants regardless of T2D diagnosis. All-cause mortality (ACM) rates among first-generation non-Western immigrants to Sweden with T2D were studied utilising data from the NDR between 2006 and 2012. In total 138,085 were diagnosed with T2D, 74.0% were native Swedes, 20.9% were first-generation immigrants and 5.1% second-generation immigrants [40]. The ACM rates were particularly low in first-generation non-Western immigrants, with the lowest rates found among ME immigrants, compared to native Swedes. Second generation immigrants did not have better survival rates [40]. This is despite the fact that ME individuals develop T2D about a decade earlier compared to native Swedes [40]. In a register-based cohort including refugees and family-reunited immigrants to Denmark between 1993-1999, ACM rates and mortality rates from CVD and cancer were significantly lower among immigrants compared to native-born Danes [41]. Immigrants to Sweden diagnosed with hypertension but without T2D were also found to have a survival advantage compared to native-born Swedes [42]. First-generation immigrants to the US were reported to have lower rates of ACM and case-specific mortality (CSM) compared to US-born individuals [43]. Advantageous survival patterns among first-generation immigrants are not only demonstrated for healthy immigrants but even those with T2D and hypertension, this survival benefit is not reproduced in second-generation immigrants suggesting that acculturation to Western culture may impact ACM and CSM in immigrants [40, 44, 45].

Diabetes, cardiovascular disease and cancer

Cardiovascular disease (CVD) and cancer disease are the leading causes of mortality worldwide and the largest contributors to the burden of chronic disease globally [46, 47]. CVD and cancer disease share a number of similar risk factors such as obesity and T2D, and both conditions including T2D are characterised by a chronic state of inflammation [46]. Atherosclerosis is no longer viewed as a disease of lipid storage but the pathogenesis is far more complex with inflammation mediating the initiation, progression and the end-stage manifestation of thrombosis in the atherosclerosis process [48]. Hypertension, smoking, dyslipidaemia and insulin resistance initiate the process of atherosclerosis by triggering the endothelial cells to express and produce adhesion molecules allowing leukocyte attachment to the vascular walls [46]. T2D is an independent risk factor for CVD, as well as both insulin resistance and hyperglycaemia are associated with low-grade inflammation with enhancement of oxidative stress, endothelial dysfunction, factors promoting platelet adhesion and atherogenesis [49].

The causal link between inflammation and cancer has been known for decades based on the observation that tumours often develop in the setting of chronic inflammation and the presence of inflammatory cells in the biopsy specimens [50]. Insulin resistance and dyslipidaemia are associated with obesity and T2D and partially explain the obesity-cancer relationship. Other mechanisms suggested to link obesity and T2D with cancer progression include an increase in insulin/IGF-1 signalling and alternating levels of adipokines such as adiponectin [51]. According to the estimation of the World Health Organization, between 30-50% of cancer cases could be prevented if certain risk factors such as tobacco use, alcohol, diets low in fruit and vegetables, obesity and inactivity could be avoided [20]. It is suggested that up to 20% of malignancies are related to weight gain and obesity and that the cancer risk increases with increasing BMI [52]. A pooled analysis of 19 population-based cohorts in East and South Asia with data from 771,297 individuals, compared individuals with diabetes at baseline with those without diabetes for the risk of death from any cancer. Baseline diabetes status was significantly associated with an increased risk of death from any cancer, but also significant associations with diabetes were observed for cancer of the colorectum, liver, bile duct, gallbladder, pancreas, breast, endometrium, ovary, prostate, kidney, and thyroid but not with haematological malignancies and lymphoma [53].

Ethnicity and cardiovascular disease

ME immigrants demonstrate a higher prevalence of T2D and obesity with both being strong risk factors for CVD, cancer disease and mortality [47, 54, 55]. It is rather surprising that in Swedish nationwide data, non-Western immigrants with T2D displayed a 30-60% lower risk of ACM, and cause-specific mortality (CSM) in cerebrovascular, diabetes-related and death from cancer [40, 42, 56] compared with natives with T2D. Studies on immigrant groups in the US and Europe have revealed ethnic differences in the incidence of CVD reporting both higher and lower incidences of CVD [41, 57, 58]. In a multi-site, multi-ethnic study from the US, 6,446 adults aged 45-84 years were included in an 11-year follow-up study examining cardiovascular health and the progression of overall cardiovascular risk over time [58]. The study showed that being foreign-born and having lived in the US for a shorter time than 10 years at baseline, were associated with better cardiovascular health and lower incidence of CVD but a faster decline in cardiovascular health over time. In another study of the incidence of CVD in 114,331 immigrants to Denmark, the incidence rates were found to be lower for the immigrants compared to Danish-born [59]. The survival rate after CVD was also reported to be better among immigrants [59]. Data from the MEDIM cohort showed no differences in self-reported prevalence of CVD between Iraqi- and Swedish-born individuals. Participants with T2D had a higher prevalence of CVD, after

adjustment for age and sex and Iraqi immigrants free from T2D had a lower prevalence of CVD compared to Swedes. T2D was an independent risk factor for CVD in Iraqis only [28]. The incidence of CVD among immigrants has also been linked to the length of stay in the host country with a higher incidence among immigrants with longer residence, which indicates acculturation towards a westernised lifestyle [58, 60].

Ethnicity and cancer

Despite the higher prevalence of T2D and obesity, lower incidence rates of cancer among ME immigrants to Europe, Australia, and Canada have been reported [61-65]. In a study by Hemminki et al. [66] on the nationwide Swedish Family-Cancer Database to analyse cancer risks in 613,000 adult immigrants to Sweden, the standardised incidence ratios for 18 cancer sites were calculated with native Swedes as reference. 110 comparisons were significant with 62 showing protection and 48 an increased risk [66]. The lowest cancer standardised incidence ratios were found among Iraqi men for all of the 18 cancer sites studied [66]. Cancer incidence data from 2005-2010 reported by The Middle East Cancer Consortium, comparing cancer incidences of Cyprus, Egypt, Israel, Jordan, Palestine, and the US [67], showed that the overall age-standardised incidence rates for males were highest in the US followed by Israeli Jews, Izmir (Turkey), Cyprus, Israeli Arabs, and lowest in Jordan [67]. Of note, Jordan is a country in the ME mainly consisting of an Arabic population. In a register study utilising data from the Danish, Finnish, Icelandic and Norwegian national cancer registries, collecting data on cancer incidence among non-Western immigrant women, reported significantly lower incidence rates of breast, colorectal and lung cancer among non-Western immigrant women compared to native women. The cancer risk was also shown to increase with the duration of residency in the host country [68].

The Role of Molecular and Hormonal Factors in Obesity and T2D

Obesity and T2D are complex diseases involving both environmental and genetic factors. Adipose tissue is more than merely adipocytes but is also an endocrine organ interacting with other hormone systems [69]. T2D and obesity are associated with low-grade inflammation resulting in abnormalities in several hormonal factors involved in the process of the metabolic syndrome [48]. Both conditions are associated with decreased levels of Vitamin D, (25(OH)D), insulin like growth factor 1 (IGF-1) and adiponectin [70]. 25(OH)D, IGF-1, and adiponectin are

reported to have a positive influence on glucose homeostasis affecting the pathways of insulin action and secretion [71-73]. A hallmark of obesity and T2D is impaired glucose and lipid metabolism and increased lipid stores in the muscle and liver which in turn are the insulin target tissues causing insulin resistance [74]. Adiponectin is a hormone secreted by adipocytes and stimulates fatty-acid oxidation leading to reduced triglyceride content resulting in a decrease in insulin resistance [74, 75]. Adiponectin has been shown to supress hepatic glucose production, thus affecting both insulin action and secretion [75]. It also inhibits inflammation and enhances cell survival [76]. However though synthesized by adipocytes in the adipose tissue, plasma adiponectin levels are reduced in obesity and T2D [77]. Pro-neurotensin (Pro-NT), the stable precursor of neurotensin is secreted by intestinal neuroendocrine cells as a response to food ingestion and facilitates lipid absorption [78]. Elevated Pro-NT levels are associated with increased T2D risk [79].

Vitamin D, PTH and glucose regulation

Vitamin D now recognised as a prohormone, was first identified in the 20th century [80]. Vitamin D, also known as calciferol, exists in two major forms, vitamin D2 (ergocalciferol) and D3 (cholecalciferol). Both forms have identical effects in the body after becoming biologically active through two enzymatic hydroxylation reactions and only differ in their side chain structure [81, 82]. Vitamin D2 is synthetic and added to foods, while D3 is synthesized in the skin from 7-dehydrocholesterol with the action of sunlight and consumed from animal-based foods [81, 82]. Circulating vitamin D and its metabolites are bound to vitamin D-binding globulin (VDBG) or albumin [83]. The first enzymatic step in the activation process takes place in the liver and is mediated by 25-hydroxalse which forms 25(OH)D, the main circulating vitamin D metabolite [84]. The second reaction takes place in the kidney mediated by 1 α-hydroxylase which converts 25(OH)D to the biologically active calcitriol (1,25-dihydroxyvitamin D) [84]. The renal activation of 25(OH)D is up-regulated by the parathyroid hormone (PTH) and down-regulated via fibroblast-like growth factor (FGF23). Low concentrations of 25(OH)D result in compensatory secondary hyperparathyroidism [83].

After becoming active, calcitriol exerts its action at a transcriptional level, regulating gene expression after binding to its receptors in the nuclei of target cells, Vitamin D receptors (VDRs) [85]. The classical actions of 25(OH)D involve regulating serum calcium and phosphate which in turn maintain bone homeostasis [86]. VDRs are found in different tissues in the body, which are not directly involved in the development and maintenance of bone health [85].

Individuals with T2D and obesity have been shown to have significantly lower levels of 25(OH)D, compared to healthy individuals [81]. Experimental and

epidemiological studies have found 25(OH)D deficiency to be associated with decreased insulin secretion, insulin resistance and T2D [87]. Potential mechanisms of how vitamin D affects glucose homeostasis include the identification of specific VDRs on both human and rat pancreatic β-cells [88]. The expression of 1-α-hydroxylase in rat pancreatic β-cells [89], and the presence of a vitamin D response element in the human insulin gene promoter have suggested potential involvement of 25(OH)D in glucose and insulin metabolism [90].

Markers of Vitamin D are known to vary by race and ethnicity. In a multi-ethnic cohort of 6,814 American adults free from cardiovascular disease between the ages of 45 and 84 years, black participants had significantly lower 25(OH)D levels and higher PTH levels compared to white participants of European ancestry [83]. A review of 41 observational studies from the MENA region, reported some of the lowest vitamin D levels worldwide [91]. In a Swedish study of immigrants from Africa and the ME to Sweden, consisting of 111 men and 106 women, 73% of the participants had insufficient or deficient Vitamin D status, [92]. Moreover, in a study of newly arrived immigrants (n=591) from Africa and Asia to Norway, the majority had 25(OH)D <50 nmol/L [93]. In a primary care centre in Sweden, Vitamin D levels were assessed in 102 patients aged 20 to 65 years, and the lowest levels were found among patients born outside of Europe [94].

The parathyroid is comprised of four glands embedded in the thyroid gland, these glands produce and secrete PTH, a polypeptide containing 84 amino acids, which maintains serum calcium homeostasis [95]. There is an inverse relationship between serum 25(OH)D and serum PTH. At low serum calcium levels, PTH mobilises calcium stores and increase calcium absorption and reabsorption. 25(OH)D and calcium exert negative feedback on the parathyroid glands to inhibit the production and release of PTH [95, 96]. Elevated level of PTH is associated with abnormal glucose metabolism and positively correlated to glucose levels and inversely related to insulin sensitivity with a higher prevalence of T2D observed in individuals with high levels of PTH [97]. In a study of 1240 blood donors, hypovitaminosis D was associated with higher BMI and high triglycerides, while PTH levels were positively associated with glucose and low density lipo protein (LDL) levels [98].

In summary, 25(OH)D deficiency, a condition linked to obesity and T2D, is common in ME immigrants. This is perhaps not only a coincidence and raises the question about potential significant ethnic differences in the associations between 25(OH)D, PTH and glucose regulation.

IGF-1 and glucose regulation

Insulin like growth factor (IGF-1) shares obvious structural homology with proinsulin, it is a 70-aminoacid polypeptide hormone, mainly produced by the liver secondary to growth hormone (GH) and insulin stimulation [99]. IGF-1 in turn provides an inhibitory feedback signal on GH secretion from the hypothalamus by stimulating the production of somatostatin in the pituitary [99]. IGF-1 is mainly known for being a growth differentiation factor but has been revealed to have several growth unrelated actions [100]. IGF-1 receptors are expressed ubiquitously in all cell types, taking part in coordinating fat, carbohydrate and protein metabolism [100]. Experiments with infusions of recombinant human IGF-1 have shown a decrease in the concentrations of glucose and insulin but also increased insulin sensitivity [101]. In a study of 116 obese subjects, BMI > 40 kg/m2 (or >35 kg/m^2 and at least one serious obesity-related health problem, such as diabetes, high blood pressure or sleep apnoea), with 41 age and sex-matched controls, IGF-1 levels were lower in obese subjects compared to the control group, the levels increased post-bariatric surgery [102]. In a longitudinal study with a cohort of 615 normoglycemic men and women 45-65 years of age, participants underwent oral glucose tolerance testing (OGTT) and IGF-1 measurements, at baseline and 4.5 years later. During follow-up, 44% developed impaired glucose tolerance and 1% T2D. Those who had IGF-1 levels below the median had a significantly reduced risk of developing both conditions [101]. However, a German and a Danish study showed that both low and high baseline IGF-1 serum concentrations are related to higher risk of developing T2D [73, 103]. In the German study, 7,777 subjects free from diabetes were followed for a time of 4.5-5 years and there were 464 cases of T2D, IGF-1 levels below the 10th or above the 90th age- and sex-specific percentile had higher risk of T2D compared with subjects having intermediate levels of IGF-1 [103]. Similar findings were reported from a Danish study of 3,354 adults, with 520 of them having insulin resistance confirmed by the homeostasis model assessment of insulin resistance (HOMA-IR), showed that both low and high levels of IGF-1 were related to higher odds of increased HOMA.IR [73]. In the face of a higher prevalence of T2D in patients with GH deficiency and in those with acromegaly, the U-shaped association seems to be likely [104, 105]. Some reports support ethnic differences in the levels of IGF-1 [105, 106]. IGF-1 has also been shown to have anti-inflammatory effects and inflammation suppresses the GH/IGF-1 axis [106]. In summary, IGF-1 seems to share not only structural but also functional homology with insulin, thus linking disturbances in IGF-1 levels to insulin resistance and inflammatory processes, making IGF-1 a relevant hormone to study in a ME population with high risk for T2D.

Adiponectin and glucose regulation

Adiponectin is an adipocyte-specific protein, i.e. adipokine. It is abundantly expressed in adipose tissue, and it is involved in glucose regulation and lipolysis since it directly sensitises insulin [77]. Hypoadiponectinemia caused by obesity seems to have a causal role in insulin resistance and T2D [107]. The adiponectin receptors have been found to be downregulated in obesity and insulin resistance conditions [108]. Upregulation of adiponectin, one of the actions of thiazolidinediones, increases insulin sensitivity [108]. The state of insulin resistance is when more insulin is required to obtain normoglycemia [108, 109]. Insulin activates a signalling network and any defects in the signalling cascade can cause insulin resistance [108, 109]. The actions of the signalling cascade of insulin are suppression of hepatic glucose production and allowing glucose transport in muscle cells and adipocytes [108]. White adipose tissue is the major site of energy storage and energy is stored in the form of triglycerides during nutritional abundance and during nutritional deprivation it is released as free fatty acids [108]. White adipose tissue has provided a survival advantage but is linked to obesity-related conditions in the abundance of nutrition [108]. Adiponectin is negatively correlated with markers of inflammation, BMI and metabolic syndrome - this has been shown in studies of subjects from different ethnic groups [110, 111]. In a study from India, 91 adults with impaired glucose tolerance were divided into two groups, one receiving standard care and the other was given advice on diet modification and exercise. OGTT was performed at baseline and one year later. A total of 25 of the participants had developed T2D, 32 had normal glucose tolerance and 34 had impaired glucose tolerance. The adiponectin levels were significantly lower in the T2D group compared to the others and no significant differences were found between the normal glucose tolerance group and the impaired glucose tolerance group [112]. In the United Arab Emirates, 206 overweight individuals with a BMI > 25, received dietary education sessions for a period of 427 ± 223 days. Adiponectin increased with decreasing BMI and waist circumference whereas male sex and T2D or a history of gestational diabetes were significantly associated with lower levels of adiponectin [112]. The sexual dimorphism in the circulating levels of adiponectin has also been reported in other studies suggesting sexual hormone regulation of the production of adiponectin and perhaps partially explaining the fact that females are more sensitive to insulin than males [113, 114]. Although the association between adiponectin, obesity and T2D is constant across ethnicities, there seem to be ethnic differences in the level of adiponectin with Europeans having higher levels of adiponectin compared to South Asians [115]. To summarise, low adiponectin levels are associated with insulin resistance, obesity and T2D, making this hormone relevant to study in a ME population with insulin resistance at high risk of developing T2D.

Pro-neurotensin and glucose regulation

Neurotensin (NT) was discovered in 1973 in bovine hypothalamus and was initially thought to be a vasodilator but was soon shown to have a dual function both as a neurotransmitter or neuromodulator in the central nervous system and functions as a hormone in the peripheral tissues [116]. NT is expressed in the central nervous system and in the gastrointestinal tract, in neuroendocrine cells [117]. NT regulates food intake or satiety and lipid absorption making it an actor in the regulation of energy balance [116, 117]. The effects of NT are mediated through three known NT receptors (NTR1, 2 and 3) [117], the receptors are heterogeneous in structure revealing the complexity of the neurotensinergic system [117]. NTR 2 and 3 are expressed in rodent β- cells and play an essential role in the survival of the cells by protecting the cells against apoptosis [116]. In the intestinal lineage of enteroendocrine cells, NT and glucagon-like peptide-1 (GLP-1), are co-expressed and then secreted in response to certain metabolites. There is evidence of NT acting synergistically together with GLP-1 to decrease the intake of palatable food and inhibit gastric emptying [116]. The concentration of NT is increased minutes after a meal, following the ingestion of fat and facilitates lipid digestion. It regulates gastrointestinal motility and pancreatic secretion [118]. In rats, both intracerebroventricular (central) and intraperitoneal (peripheral) injection of NT reduces food intake [119]. Studies have shown that the regulation of NT is disturbed in human obesity and has trophic effects on neoplastic tissue, NTR1 is expressed in ductal breast cancer tumours [120]. Mature NT is unstable in vitro and vivo, which makes it hard to measure, the N-terminal part of the prepro-neurotensin precursor hormone is measured and referred to as Pro-neurotensin (Pro-NT) [120]. In the population-based Malmö Diet and Cancer Study, Pro-NT was measured in plasma from 4,632 fasting participants at baseline with a median follow-up ranging from 13.2 to 15.7 years, Pro-NT was significantly higher in women compared to men, and increased Pro-NT was associated with the development of T2D, CVD, total mortality, cardiovascular mortality, and breast cancer in women [120]. In the MEDIM cohort, the levels of Pro-NT in ME-born individuals were shown to be higher than among Swedish-born individuals, and an association was found between the levels of Pro-NT and impaired glucose regulation among ME-born subjects [121]. In the MEDIM culturally adapted lifestyle intervention study, the levels of Pro-NT increased with lifestyle intervention and weight loss in ME subjects at high risk of T2D [122]. Pro-NT has also been shown to have anti-inflammatory and anti-oxidative properties with higher levels associated with inflammatory conditions such as inflammatory bowel disease [123].

In summary, Pro-NT is positively associated with impaired glucose regulation, and it is of interest to study whether the improvement in insulin sensitivity as a result of lifestyle intervention is mediated by changes in the levels of Pro-NT.

Aims

The overall aim of this thesis was to understand the pathophysiological processes prior to the development of type 2 diabetes among ME immigrants in Sweden. To assess the overall risk of metabolic syndrome, all-cause mortality, cardiovascular disease and cancer and to study the potential role of extra pancreatic molecular factors, for example Vitamin D, on the pathophysiology of the disease.

Given the differences in insulin action and secretion shown from the MEDIM cohort between ME and European ancestry, we hypothesised significant ethnic differences in the levels of Vitamin D and consequently Parathyroid hormone. The study-specific aims were as follows:

Paper I: To study if ageing influences insulin secretion and action measured in Middle Eastern immigrants and native Swedes. In addition, we aimed to study whether the potential effects of age were modified by ancestry.

Paper II: Based on the MEDIM cohort the aim was to study if ME ethnicity influences all-cause mortality, incidence of cancer and cardiovascular disease, and case-specific mortality after adjustment for anthropometrical measures, and lifestyle behaviour.

Paper III: To compare the levels of Vitamin D and parathyroid hormone between Middle Eastern immigrants from Iraq and Swedish-born individuals, and to explore potential ethnic differences in how Vitamin D and parathyroid hormone influence insulin action and secretion.

Paper IV: In ME immigrants at high risk of developing type 2 diabetes from the MEDIM cohort, we aimed to study the effect of a culturally adapted lifestyle intervention on the levels of Vitamin D, IGF-1, and adiponectin, and to study the potential effect of these hormones including Pro-NT on insulin action and secretion.

Materials and Methods

The dissertation is based on two studies namely the MEDIM population-based study (Papers I-III) and the MEDIM intervention study (Paper IV).

Table 2.
Overview of the papers.

Paper	I	II	III	IV
Design	Cross-sectional	Longitudinal	Cross-sectional	RCT
Year	2010-2012	2010-2018	2010-2011	2015
Participants	Born in Iraq (n=1,212) Born in Sweden (n=704)	Born in Iraq (n=1,375) Born in Sweden (n=728)	Born in Iraq (n=469) Born in Sweden (n=449)	Born in Iraq (n=67)
Outcomes	Ethnic differences in ISI and DIo with increasing age	ACM, incidence of cancer, CVD and CSM	Ethnic differences in the levels of 25(OH)D and PTH, effect on ISI and DIo	Effect of lifestyle intervention on 25(OH)D, IGF-1, adiponectin and Pro-NT and the hormonal effect on ISI and DIo
Data collection methods	OGTT, clinical exams, anthropometrical data, questionnaires and laboratory analyses	OGTT, clinical exams, anthropometrical data, questionnaires, laboratory analyses, data from NDR, NPR, and CDR	OGTT, questionnaires and laboratory analyses	OGTT, clinical exams, questionnaires and laboratory analyses
Data analysis	Linear regression	Cox regression analysis	Linear regression	Linear mixed model

RCT= Randomised Controlled Trial, ISI=Insulin Sensitivity Index, DIo=Oral Disposition Index, ACM=All Casuse Mortality, CVD=Cardiovascular Disease, OGTT= Oral Glucose Tolerance Test, NDR= National Diabetes Register, NPR= National Patient Register, CDR= Cause of Death Register.

The MEDIM population-based study

The MEDIM study is a population-based, cross-sectional study carried out between 2010 and 2012 in Malmö, Sweden. Malmö is the third largest city in southern Sweden with a population of 362,133 residents (31 December 2023) [20]. About 30% of the population in Malmö is born outside of Sweden and the largest immigrant group is born in the ME with a population of 11,645 individuals born in Iraq (2023) [20]. A random sample of residents in Malmö born in Iraq or Sweden aged 30-75 years old were selected from the census register. Iraqi and Swedish-born lived in the same geographical area and were age and sex-matched. A total of 2,924 Iraqis and 2,372 Swedes were informed about the study by phone and mail. Individuals with severe mental and physical illness, which would prevent them from participating in the study, individuals with type 1 diabetes, and pregnant women were excluded. Participants were given both oral and written information in their native language (either Arabic or Swedish), prior to participation. After agreeing to participate, they were asked to sign an informed consent form. Figure 2 shows a flowchart describing the recruitment of MEDIM participants and participation rate. The study achieved a participation rate of 64% in Iraqis and 40% in Swedes.

In all participants, a health examination was conducted by educated bilingual (Arabic and Swedish) research nurses, including anthropometrics, fasting blood samples and an oral glucose tolerance test (OGTT) [124]. Due to ethical considerations, people with known T2D did not undergo OGTT in order not to be exposed to hyperglycaemia. Participants were advised to fast for 10 hours prior to the health examination. Sociodemographic and lifestyle behaviour data were collected using self-administered questionnaires in both Arabic and Swedish. Questionnaires were filled out by the participants providing information on lifestyle habits, family history of diabetes, previous diagnosis of T2D, cancer, previous diagnosis of CVD as well as present medication, and dietary habits according to the Nordic Nutrition recommendations [125]. Participants were examined in parallel throughout the study period. They were asked how many standard glasses of alcohol they usually consumed during an average week. Those consuming any amount of alcohol were considered alcohol consumers. Current smoker was defined as smoking at least one cigarette per day (tobacco 1 g/day) and lasting for at least six months.

Physical activity was reported by the participants using the questionnaire developed by the Swedish National Board of Health and Welfare [126]. The participants were asked to report time spent in physical activities of strenuous and non-strenuous nature during a regular week and were given examples of the types of activities defined as strenuous and non-strenuous. The time spent in strenuous activities was doubled and added to the time spent in non-strenuous activities during a week.

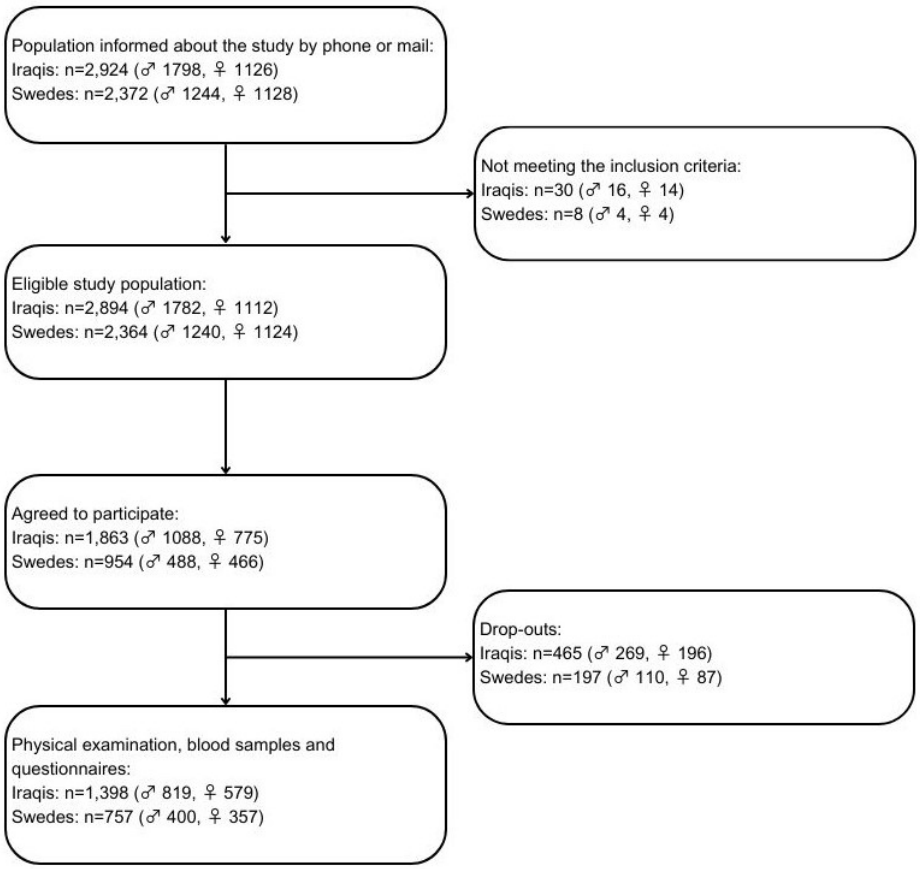

Figure 2: Flowchart representing recruitment of participants in the MEDIM study.

Laboratory analysis and definitions

A HemoCue photometer (HemoCue AB, Ängelholm, Sweden) was used to measure plasma glucose levels. Fasting reference ≥ 7,0 mmol/l, taken twice capillary and non-fasting capillary 2h glucose ≥ 12,2 mmol/l were the WHO criteria for a diabetes diagnosis [127, 128]. Radioimmunoassay (Access© Ultrasensitive Insulin, Beckman Coulter, USA) and high-pressure liquid chromatography (Bio-Rad) were used to estimate serum insulin levels and HbA1C [127]. Enzymatic methods were used to estimate plasma HDL-cholesterol (Boehringer Mannheim GmbH, Germany) and triglyceride levels (Bayer Diagnostics) [129] whereas Friedewald's equation was used to estimate plasma LDL-cholesterol levels [130].

In studies III and IV, serum concentrations of 25(OH)D were assessed by a chemiluminescence immunoassay and expressed in nmol/L [131]. 25(OH)D insufficiency was defined as mild (serum 25(OH)D < 50 and ≥ 25 nmol/L), moderate (serum 25(OH)D < 25 and ≥ 12.5 nmol/L) and severe deficiency (< 12.5 nmol/L) [132].

PTH was analysed using the Atellica IM PTH-method and measured in pmol/L, ref: 2,0-8,5 pmol/L [133].

In study IV, an in-house Radioimmunoassay (RIA) was used for the quantitative measurement of levels of IGF-I expressed in µg/L in serum after separation of IGFs from IGFBPs [134]. In-house time-resolved immunofluorometric assay (TR-IFMA) based on commercial antibodies was used for the quantitative determination of serum Adiponectin expressed in mg/l [135]. Pro-NT was measured using a chemiluminescence-based immunoassay.

Oral glucose tolerance test (OGTT)

Participants free from T2D were tested using a glucose tolerance test (OGTT). The test is used to determine the ability to use and store glucose normally and it is the gold standard for the diagnosis of diabetes [128, 136].

Insulin sensitivity index (ISI), insulin secretion (corrected insulin response, CIR) and DIo (Oral disposition index) were assessed via insulin and glucose measured at 0, 30 min, 60 min and 120 min during OGTT (Matsuda indices) [124, 137, 138]. ISI, insulin sensitivity index by Matsuda provides an estimate of hepatic and muscle insulin sensitivity.

ISI = 10,000/√ [(f-glc (mmol/L) × f-insulin (mIE/L)) × (mean OGTT glc conc. (mmol/L) × mean OGTT insulin conc. (mIE/L))] [124].

CIR (Corrected Insulin Response) is assessed to measure glucose-stimulated insulin secretion and provides an estimate of beta-cell function. CIR was calculated from OGTT as follows:

CIR = (100 × insulin at 30 min (mIE/L)/(glc30 (mmol/L) × (glc30–3.89 mmol/L)) and requires that glucose at 30 min (glc30) > 4.44 mmol/L and glc30 > f-glc [124, 137, 139].

DIo is an estimate of beta-cell function adjusted for insulin resistance. DIo is the product of CIR and ISI, with ISI corresponding inversely to insulin resistance.

Paper I

In total, ISI was assessed in 1,212 Iraqi and 704 Swedish-born participants whereas DIo was assessed in 1,193 Iraqi and 688 Swedish-born participants who were included in the analysis. The exclusion after OGTT was due to CIR criteria requiring glucose levels at 30 min (glc30) > 4.44 mmol/L and at glc30 > f-glc.

Paper II

The time of observation of the study participants was from the day of enrolment in the MEDIM baseline study until the 31st of December 2018. Information on cardiovascular events, cancer diagnoses and cause of death were retrieved from the National Patient Register (NPR) and the Cause of Death Register (CDR).

In this study, the ICD 10 (International Statistical Classification of Diseases and Related Health Problems 10th revision) was used with codes from chapter C for cancer disease and chapter I (Disease of the circulatory system) for CVD. Death from cancer was defined as having a code from chapter C and death from CVD as having a code from chapter I on the death certificate.

ICD 10 codes I210, I211, I214, I213, I219, I220 and I252 defined myocardial infarction and I259 (Chronic ischaemic heart disease, unspecified) was additionally included when defining death from disease of the circulatory system. ICD 10 codes I613, I619, I629, I634 and I639 defined stroke.

The outcomes studied were ACM, a composite of either death from cancer or incidence of cancer, and a composite of either death from CVD or incidence of CVD. CVD included coronary heart disease (angina pectoris and myocardial infarction), cerebrovascular (cerebral infarction, cerebral haemorrhage, transitory ischaemic attack), claudicatio intermittens and cardiovascular death.

The association of these outcomes with country of birth were studied, adjusting for age, sex, anthropometrical measures (BMI) and lifestyle (smoking, intake of fruit and berries and/ or vegetables and alcohol consumption). When studying incidence of CVD morbidity and mortality individuals reporting a history of CVD, a CVD diagnosis before the date of inclusion, a diagnosis of old myocardial ischemia (ICD 10 code of I252) and those diagnosed with late effects of cerebral infarction (ICD 10 code I693) were also excluded.

When studying the incidence of cancer events and cancer death, individuals with a history of cancer diagnosis prior to the date of study participation were excluded.

From the MEDIM cohort, 23 Iraqis were excluded for reporting cancer at baseline and 51 for CVD, for Sweden-born participants 29 were excluded for reporting cancer and 48 for CVD at baseline. Included in the analysis were 1,375 for cancer and 1,347 for CVD among Iraqis and among Swedes, 728 for cancer and 709 for CVD.

Paper III

The 25(OH)D and PTH were analysed in participants recruited from the start of the MEDIM study (February 2010) until December 2011. The original MEDIM study ended in Dec 2012 but during 2012 only Iraqi participants were recruited. However, to allow comparison between Iraqis and Swedes and to avoid the influence of seasonal variation, 25(OH)D and PTH were analysed in those recruited during the same period, i.e. a total of 918 participants (469 Iraqis and 449 Swedes).

Paper IV

The MEDIM intervention study

The MEDIM RCT culturally adapted lifestyle intervention study was conducted in 2015 for a duration of four months. Iraqi-born individuals at high risk for developing T2D from the MEDIM cohort were invited to participate. At high-risk was defined as having a BMI ≥28 kg/m2 and/or waist circumference (≥80 cm in women and ≥ 94 cm in men) [122, 140] and/or pre-diabetes, i.e. impaired fasting plasma glucose (IFG) defined by The World Health Organization (FPG: 6.1-6.9 mmol/l and 2-h glucose < 7.8 mmol/l), impaired glucose tolerance (IGT) (FPG < 6.1 mmol/l and 2-h glucose: 7.8-11 mmol/l) or impaired glucose regulation (FPG: 6.1-6.9 mmol/l and 2-h glucose: 7.8-11 mmol/l) [122]. A total of 636 Iraqi-born individuals were invited (40% of the Iraqi-born participants in the MEDIM cohort) of which 104 accepted to

participate and 96 were found eligible for participation in the study, corresponding to a participation rate of 15.1% [122]. Figure 3 is a flowchart of the participation and randomisation processes. In total 7.7% (n=8) of the initial 104 participants were diagnosed with diabetes on the first visit and excluded from the study. Using a random number generator in the statistical software SPSS, the participants were randomised -following their first health examination - either to control or to the intervention with a 1:1 allocation ratio. Men and women were randomised separately but couples were randomised into the same group to avoid information transfer between the groups. The nurses performing the health examinations were blinded as to the participants' group status. The remaining 96 participants were randomised to the intervention (n=50) or to the control group (n=46). The groups were similar in age and sex distribution. In the original study protocol, the follow-up time was planned to six months with 10 group sessions [141]. However, due to the occurrence of the month of Ramadan, with dietary fasting during daytime, the mean follow-up time was shortened.

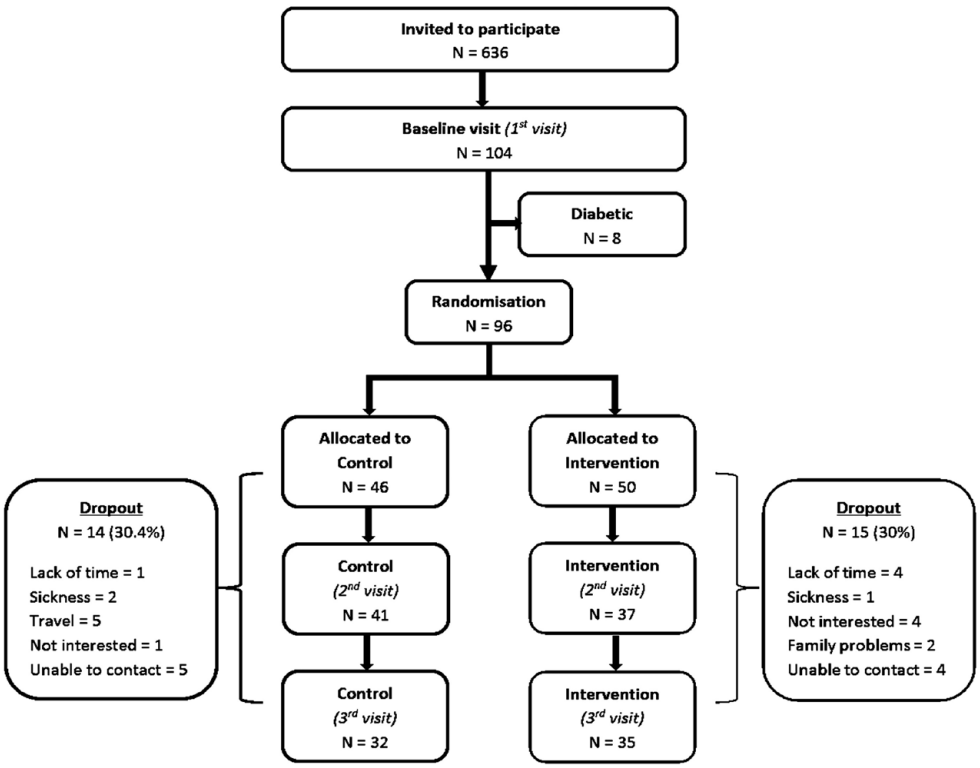

Figure 3: Recruitment and flow of participants in the MEDIM intervention study, by Siddiqui et al [122].

The intervention comprised of seven group sessions and a cooking class, with a focus on diet and physical activity, and the cultural adaptation included gender-specific group sessions. At all meetings a diabetes nurse and health coach familiar with ME culture were present, and all language translation was performed by a professional Arabic translator [122, 141]. Financial support for admission to physical activity and sports clothes was offered, the participants received education in the relation between T2D and lifestyle habits as well as dietary habits. Socio-cultural barriers to physical activity were addressed, and female participants were informed about females-only activity centres. The participants were introduced to dietary recommendations by the Swedish food agency, and they were asked to bring the recipe of their favourite dish to the cooking class where it was cooked in a healthier way by a professional chef familiar with cooking diabetes-friendly diets. Traditional food and cooking methods were discussed and knowledge gaps in the understanding of the association between T2D and lifestyle were addressed [122, 141].

The study included three health examinations and took place between mid-January (visit 1) and mid-June 2015 (visit 3). Trained study nurses, who could speak Arabic and Swedish, conducted physical examinations and collections of fasting blood samples and oral glucose tolerance tests (OGTT; 75 g glucose) at each health examination. At the second visit 41 participated from the control group and 37 from the intervention group, at the third visit 32 from the control group and 35 from the intervention group, which is approximately 30% dropout from both groups due to lack of time, sickness, travel, not interested, family problems or unable to contact. The participants were asked to fill in a four-day food diary in connection with each health examination and the data were then processed in the Dietist XP software version 3.2 to obtain mean caloric intake.

Physical activity was self-reported by the participants using the ‘International Physical Activity short form Questionnaire’ (IPAQ) [142]. The energy expenditure of vigorous and moderate-intensity physical activity as well as walking was reported as ‘metabolic equivalent of task’ (MET). No differences were made between indoor and outdoor physical activity. MET-hours/week were calculated by multiplying the time spent performing the activities during the week with MET values of 8 METS for vigorous activity, 4 METS for moderate physical activity and 3.3 METS for walking. At the first and the third health examination visits, the serum concentrations of 25(OH)D, IGF-1, adiponectin, and Pro-NT were analyzed.

Ethical considerations

All participants of the MEDIM cohort provided written informed consent and the Ethics Committee at Lund University approved the study (No. 2009/36 & 2010/561), for study number I-IV of this project. Ethical permission was also obtained for access to register data in the second study (No. 2019/01166) as well as permission for the intervention study, study number IV (No. 2011/88). The studies conform to the principles outlined in the Declaration of Helsinki [143]. Newly discovered cases of diabetes were referred to their own physician for management and the participants were given information regarding their blood test results in the original MEDIM cohort. Participants in the intervention study, which were randomised to the control group, were given usual care advice on a healthy lifestyle similar to the advice given to the patients in a primary care setting.

Statistical analyses

For all the studies data were presented in means (standard deviation, SD), numbers (percentages) or for skewed data, medians (interquartile range, IQR). All tests were two-sided and a p-value of < 0.05 was considered statistically significant. Skewed variables were log/ln-transformed before analysis to approximate normal distributions.

Paper I

Analyses were performed using IBM SPSS Statistics 26. The total study population was divided into four age categories based on quartile cut points with approximately 540 individuals in each age category: < 39 years, $39 \geq$ to $< 46 \geq$ to < 55 years and $>$ 55 years. Independent sample Median tests were used to compare the levels of insulin secretion and insulin sensitivity across groups. Multiple linear regression models were used to explore the associations between insulin secretion, insulin sensitivity (dependent variables) β coefficients with 95% confidence intervals, and country of birth, age, sex, BMI, physical activity, and tobacco as independent variables.

Paper II

Analyses were performed using IBM SPSS Statistics 28.0, the follow-up time was from the date of inclusion 2010-2012 until 31st of December 2018. Log-rank test was used to compare incidence rates and Cox regression for survival analysis, 95.0% CI for Exp(B). The continuous variables age and BMI were adjusted for assessing

both linear and quadratic terms. The proportional hazard assumption was assessed in all the Cox regression models by adding an interaction term between follow-up time and country of origin. The hazard ratios (HR) were adjusted for age, sex, anthropometric measures, lifestyle habits and current diagnosis of T2D, cancer and CVD.

Paper III

Statistical analyses were performed using IBM SPSS version 29.0. Multiple linear regression models were used to explore the associations between insulin secretion, insulin sensitivity (dependent variables), β coefficients with 95% confidence intervals, and other covariates as independent variables. Multiple linear regression models were also used to study the differences in 25(OH)D and PTH between the groups, adjusting for the confounding effects of relevant variables (country of origin, age, sex, BMI, dietary habits, and physical activity).

Paper IV

Statistical analyses were performed using IBM SPSS version 28.0. Only subjects participating in all visits, i.e. one to three are included. Groups were compared using an independent sample T-test for normally distributed variables and Mann-Whitney U test for non-normally distributed continuous variables. Fisher's exact test or chi-square test were used for categorical variables. The effect of the changes in the levels of 25(OH)D, IGF-1, adiponectin, and Pro-NT on ISI and DIo were studied using linear mixed-effects model analysis and expressed as β-coefficient percentage change (calculated as 100*(exp β-1) in the outcomes per month in the intervention group compared to the control group. Fixed effects were used to control for any participant-specific attributes that do not vary across time; a time variable was included for potential changes over time that might have occurred in both groups and an interaction variable between group and time to account for any effects imposed by the intervention.

Results

Paper I

Baseline insulin secretion represented by DIo and insulin action represented by ISI for each group are described in Table 3. Insulin secretion and action decreased with increasing age in both the Iraqi and Sweden-born groups, Figure 4-5. DIo decreased with increasing age in the total study population (β for the effect of age on ln DIo: -0.018, CI -0.023 to -0.013, P<0.001), adjusted for origin, lifestyle and anthropometric measures. No significant interaction was observed between country of birth and age. Iraqi immigrants had generally lower DIo in all age categories compared to native Swedes, (median: 12,712.9 vs. 14,659.2, P=0.004) but the differences were not significant after adjusting for BMI, the β coefficient was reduced by approximately 50% after adjustment for this variable, reflecting that being overweight has a great effect on insulin secretion.

ISI was significantly lower in Iraqi immigrants than in native Swedes, after adjusting for covariates in the full model (Table 4). As Figure 4 illustrates, the decline in ISI seems to be rather biphasic, with the decline being more stable among Swedish-born until the age of 55 years when a sharper drop is noticed. On the other hand, the drop in ISI levels stabilises after the age of 55 years for the Iraqi participants. There was no significant interaction between country of birth and age on ISI (P= 0.587). The median level of ISI among the youngest Iraqi-born immigrants (< 39 years of age) was even lower than the median level of ISI among the oldest Swedish-born participants (> 55 years of age, 85.98 vs 88.90, P=0.001), (Table 3). Across all age groups, the Iraqi immigrant population displayed significantly lower median levels of ISI compared to the Swedish population even after adjusting for sex and BMI, (<39 years of age, 85.8 vs 111.7, P=0.014), (39-46 years of age, 77.2 vs 107.7, P=0.001), (46-55 years of age, 70.8 vs 107.4, P=0.001), (> 55 years of age, 70.5 vs 88.9, P=0.009).

Table 3:
Median levels of insulin secretion and action among Iraqis and Swedes from the MEDIM cohort.

Variable	Country of Birth	
	Iraq (n= 1193)	Sweden (n= 688)
ISI (mmol/L*mIE/L−1)	76.9	102.3
CIR (mmol/L*mmol/L*mIE/L−1)	169.67	147.64
DIo (mmol/L*mmol/L*mmol/L)	12,712.9	14,659.2

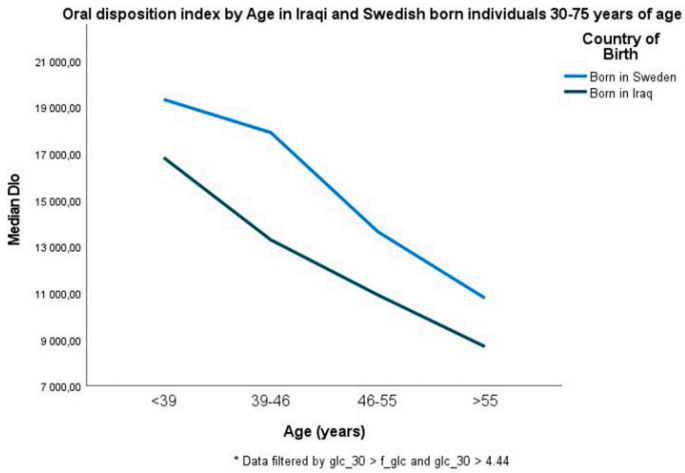

Figure 4: By Nadine et al [144], DIo by age in Iraqi and Swedish born individuals.

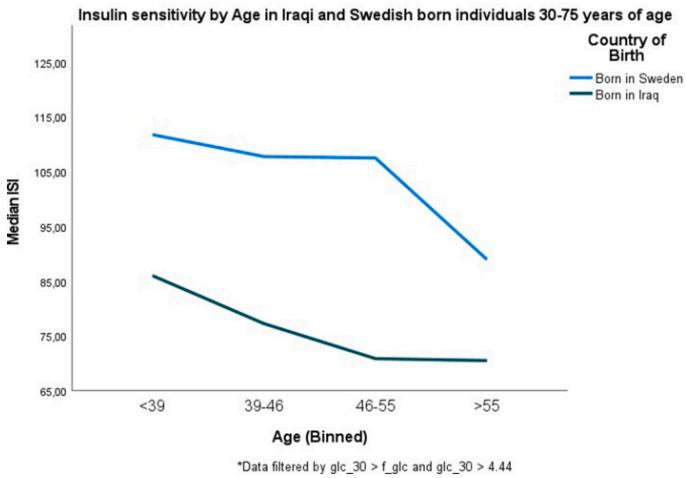

Figure 5: By Nadine et al [144], ISI by age in Iraqi and Swedish born individuals.

Table 4:
Linear regression models with ln ISI as a dependent factor expressed as β coefficients with 95% confidence intervals.

Variable	Model 1 N = 1915 R^2= .047	Model 2 N = 1854 R^2= .091	Model 3 N = 1852 R^2= .307	Model 4 N = 1654 R^2= .327
Born in Sweden **Born in Iraq**	Reference -.288*** -.346 to -.230	Reference -.281*** -.342 to -.221	Reference -.151*** -.205 to -.097	Reference -.093** -.154 to-.032
Age (years)		-.005** -.008 to -.002	-.003* -.005 to .000	-.003** -.006 to .001
Female sex **Male sex**		-.227*** -.283 to -.171	-.245*** -.294 to -.196	-.263*** -.315 to -.211
Family history of diabetes **Yes** **No**		-.015** -.026 to -.004	-.008*** -.018 to .002	-.006 -.017 to .004
Body mass index (kg/m^2)			-.066*** -.072 to -.061	-.065*** -.071 to -.059
Hours physically active/week				.034*** .023-.046
Current tobacco smoking				.044 -.017-.104

P<0.05*, P< 0.01**, P<0.001***.

Paper II

The baseline characteristics of the Iraqi and the Swedish groups are presented in Table 5. Table 6 shows a Cox regression analysis, the HR of ACM was 68% lower in Iraqi immigrants than in native-born Swedes (HR=0.32; 95% CI 0.13-0.79, $p<0.05$) after adjustments for country of origin, age, sex, BMI, the diagnosis of T2D, CVD, cancer at baseline and lifestyle behaviours. Figure 6 shows the survival rate in the fully adjusted model. We found a lower incidence of cancer disease and cancer mortality in Iraqi-born as compared to Swedish-born individuals, Table 7. The HR was 61% lower (.39; CI .22-.69, $p<0.01$) in the fully adjusted model, Figure 7.

A 44% lower incidence of CVD and CVD mortality in Iraqi-born as compared to Swedish-born individuals was observed (HR .56; CI .33-.95, $p<0.05$) in the fully adjusted model, Table 8 and Figure 8.

Table 5:
Characteristics of study participants (Iraqi-and Swedish-born living in Malmö).

Variable	**Country of Birth**		
	Iraq (n=1398)	Sweden (n=757)	P-value
Hypertension[1], n (%)	165 (12.5)	118 (16)	0.026
Blood pressure lowering agents, n (%)	164 (12.6)	114 (15.4)	0.074
T2D[2], n (%)	171 (12.8)	54 (7.2)	<0.001
T2D treatment, insulin, n (%)	7 (13)	18 (11.1)	0.8
T2D treatment, GLM[3], n (%)	89 (54.9)	16 (29.6)	0.002
Cancer[4], n (%)	23 (1.7)	29 (3.9)	0.002
CVD[5], n (%)	51 (3.8)	48 (6.4)	0.007
Total cholesterol (mmol/L)	4.9 (1.0)	5.2 (1.0)	<0.001
p-LDL (mmol/L)	3.2 (0.8)	3.3 (0.9)	0.340
p-HDL (mmol/L)	1.2 (0.3)	1.4 (0.5)	0.004
p-Triglyceride (mmol/L)	1.6 (1.0)	1.3 (0.8)	0.410
Use of lipid lowering agents, n (%)	85 (6.5)	64 (8.6)	<0.001
Diet[6], n (%)	105 (7.9)	91 (12.2)	0.002
Alcohol, n (%)	239 (17.9)	606 (81.1)	<0.001

Crude data are presented as means (SD) or as numbers (percentages); LDL/HDL is low-density/high-density lipoprotein.[1]Hypertension at baseline, [2] T2D at baseline, [3]Glucose lowering medication, [4]Cancer disease at baseline, [5]CVD at baseline, [6]Daily intake of fruit, berries and/or vegetables.

Table 6:
Cox regression models showing adjusted HR of ACM, model 1-5, 95.0 % CI for Exp(B).

	Model 1	Model 2	Model 3	Model 4	Model 5
Born in Iraq	.26 (.12-.54)***	.41 (.19-.87)**	.38 (.18-.83)**	.38 (.17-.83)*	.32 (.13-.79)*
Age[1] (years)		.98 (.71-1.35) 1.00 (.99-1.00)	.96 (.69-1.32) 1.00 (1.00-1.04)	.93 (.68-1.29) 1.00 (1.00-1.04)	.89 (.63-1.22) 1.00 (1.00-1.01)
Sex (male)		1.34 (.67-2.68)	1.44 (.71-2.93)	1.41 (.70-2.87)	1.31 (.63-2.72)
BMI[2]			1.03 (.65-1.64) 1.00 (.99-1.01)	.99 (.62-1.59) 1.00 (.99-1.01)	1.04 (.64-1.68) 1.00 (.99-1.01)
T2D[3]				1.41 (.61-3.28)	1.43 (.62-3.31)
CVD[4]				2.17 (.92-5.10)	1.94 (.83-4.53)
Cancer[5]				1.69 (.62-4.63)	1.80 (.65-4.94)
Smoking[6]					2.38 (1.16-4.90)*
Diet[7]					1.71 (.85-4.70)
Alcohol					.65 (.30-1.35)

[1]Linear age and age squared, [2]Linear BMI and BMI squared, [3]T2D at baseline, [4]CVD at baseline, [5]Cancer disease at baseline, [6] Current tobacco smoking, [7]Daily intake of fruit, berries and/or vegetables, P<0.05*, P< 0.01**, P<0.001***.

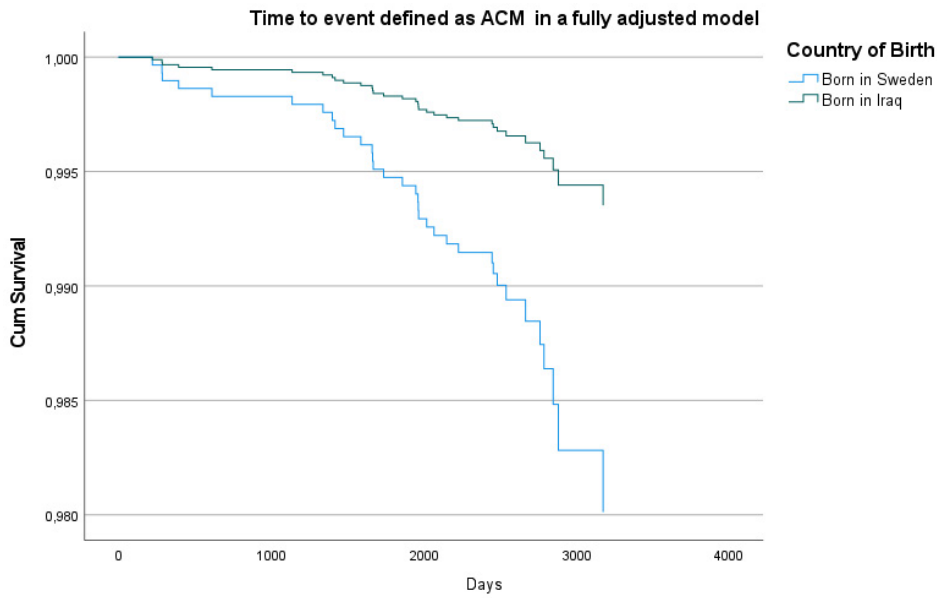

Figure 6: By Nadine et al [145], time to event defined as ACM in Iraqi and Swedish born individuals.

Table 7:
Cox regression models showing adjusted HR of cancer events and death from cancer
Model 1-5, 95.0 % CI for Exp(B).

	Model 1	Model 2	Model 3	Model 4	Model 5
Born in Iraq	.28 (.18-.44)***	.37 (.23-.59)***	.34 (.21-.55)***	.35 (.22-.57)***	.39 (.22-.69)**
Age[1] (years)		1.31 (1.05-1.00)** 1.00 (.99-1.00)	1.32 (1.05-1.65)** 1.00 (.99-1.00)	1.32 (1.05-1.65)* 1.00 (.99-1.00)	1.31 (1.04-1.64)* 1.00 (.99-1.00)
Sex (male)		.85 (.56-1.31)	.81 (.53-1.25)	.80 (.52-1.23)	.74 (.47-1.17)
BMI[2]			1.25 (.81-1.92) 1.00 (.99-1.00)	1.23 (.80-1.90) 1.00 (.99-1.00)	1.39 (.85-2.26) 1.00 (.99-1.00)
T2D[3]				.72 (.36-1.44)	.77 (.38-1.53)
CVD[4]				1.78 (.90-3.50)	1.77 (.89-3.52)
Smoking[5]					1.10 (.67-1.81)
Diet[6]					1.31 (.84-2.05)
Alcohol					1.05 (.62-1.80)

[1]Linear age and age squared, [2] Linear BMI and BMI squared, [3] T2D at baseline, [4]CVD at baseline, [5]Current tobacco smoking, [6] Daily intake of fruit, berries and/or vegetables, P<0.05*, P< 0.01**, P<0.001***.

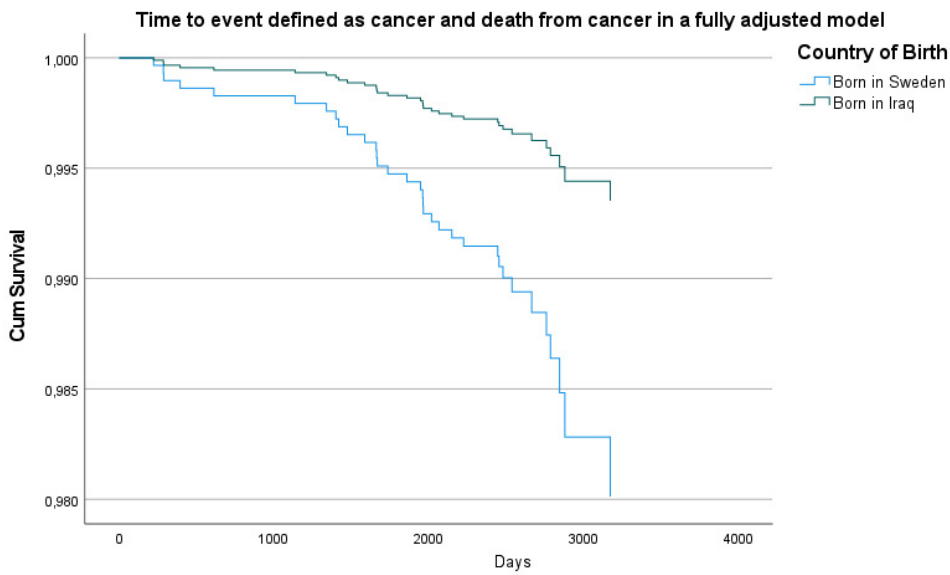

Figure 7: By Nadine et al [145], time to event defined as cancer and death from cancer in Iraqi and Swedish born individuals.

Table 8:
Cox regression models showing adjusted HR of CVD events or death from CVD, model 1-5, 95.0 % CI for Exp(B).

	Model 1	Model 2	Model 3	Model 4	Model 5
Born in Iraq	.61 (.41-.90)*	.82 (.54-1.22)	.74 (.49-1.12)	.66 (.43-1.02)	.56 (.33-.95)*
Age[1] (years)		1.49 (1.18-1.88)*** 1.00 (.99-1.00)**	1.47 (1.17-1.86)** 1.00 (.99-1.00)*	1.45 (1.15-1.84)** 1.00 (.99-1.00)*	1.43 (1.13-1.82)** 1.00 (.99-1.00)*
Sex (male)		1.53 (1.00-2.32)*	1.50 (.98-2.28)	1.48 (.97-2.27)	1.55 (.99-2.43)
BMI[2]			1.44 (.94-2.22) .99 (.99-1.00)	1.49 (.96-2.32) .99 (.99-1.00)	1.53 (.97-2.41) .99 (.99-1.00)
T2D[3]				1.80 (1.10-2.97)*	1.72 (1.04-2.86)*
Hypertension[4]				1.09 (.67-1.77)	1.21 (.74-1.98)
Cancer[5]				1.37 (.58-3.21)	1.42 (.61-3.34)
Smoking[6]					1.50 (.97-2.33)
Diet[7]					1.07 (.71-1.62)
Alcohol					.75 (.45-1.24)

[1]Linear age and age squared, [2]Linear BMI and BMI squared, [3]T2D at baseline, [4]Hypertension at baseline, [5]Cancer at baseline, [6]Current tobacco smoking, [7]Daily intake of fruit, berries and/or vegetables, P<0.05*, P< 0.01**, P<0.001***.

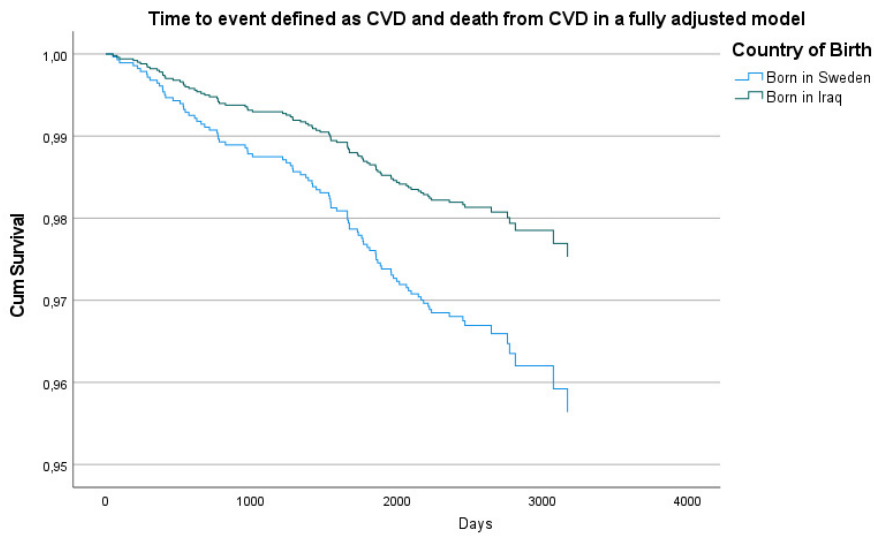

Figure 8: By Nadine et al [145], time to event defined as cancer and death from cancer in Iraqi and Swedish born individuals.

Paper III

In total 25(OH)D and PTH were analysed in 918 men and women (449 Swedes and 469 Iraqis) from the MEDIM cohort. Table 9 shows the differences in the levels of 25(OH)D and PTH between the groups related to sex and diagnosis of T2D. In total, 22.3% of the Iraqi-born participants had 25(OH)D levels < 25nmol/L, but only 7.7% of this group had elevated PTH values > 8.5pmol/L. Figure 9 illustrates the distribution of the 25(OH)D levels based on the country of origin, with dominance of the Iraqi group in the lower 25(OH) categories. Table 10 shows significant differences in ISI between the groups but in Model 5, the differences in ISI were no longer significant when adjusted for 25(OH)D. No differences in insulin secretion were observed between the groups.

The adjusted levels of 25(OH)D as well as PTH differed significantly between the groups, with the Iraqi-born participants having significantly lower levels of 25(OH)D and higher levels of PTH. Table 6 further illustrates that 96% of the Iraqis with T2D had 25(OH)D levels < 50 nmol/L and almost 22% of the Iraqi individuals had 25(OH)D levels < 25 nmol/L.

Table 9:
Descriptives of 25(OH)D and PTH levels among the participants.

Variable	Country of Birth		
	Iraq (n=469)	Sweden (n=450)	P-value
25(OH)D[1] nmol/L	29 (25, 35)	52 (40, 63)	<0.001
25(OH)D[1] male sex	29 (25, 35)	51 (39, 62)	<0.001
25(OH)D[1] female sex	28 (25, 34)	53 (41, 64)	<0.001
25(OH)D < 25 nmol/L (%)	105 (22.3)	7 (1.6)	<0.001
25(OH)D < 50 nmol/L (%)	432 (92.1)	204 (45.3)	<0.001
T2D and 25(OH)D < 50 nmol/L	52 of 56	11 of 26	<0.001
PTH (SD) pmol/L	5.1 (2.3)	3.8 (1.6)	<0.001
PTH (SD), male sex	5.3 (2.9)	4.0 (1.5)	<0.001
PTH (SD), female sex	4.8 (2.1)	3.6 (1.6)	<0.001
PTH > 8.5 pmol/L (%)	36 (7.7)	6 (1.3)	<0.001

Crude data are presented as means (SD) or as numbers (percentages); [1]Differences in medians between the groups (IQR).

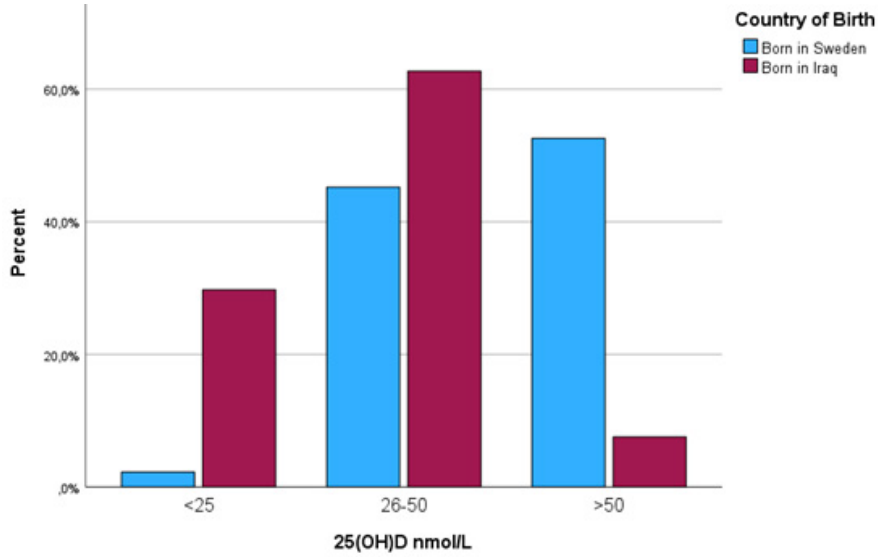

Figure 9: By Nadine et al [146], the distribution of 25(OH)D levels based on the country of origin.

Table 10:
Linear regression models with ln ISI as a dependent factor expressed as β coefficients with 95% confidence intervals.

Variable	Model 1 N = 831 R^2= .032	Model 2 N = 831 R^2= .297	Model 3 N = 808 R^2= .299	Model 4 N = 808 R^2= .545	Model 5 N = 808 R^2= .300
Country of origin	Reference -.222*** -.305 to -.139	Reference -.089* -.162 to -.016	Reference -.085* -.160 to -.010	Reference -.085* -.163 to -.007	Reference -.058 -.150 to .033
Age (years)		-.001 -.004 to .003	-.001 -.004 to .003	-.001 -.004 to .003	-.001 -.005 to .003
Sex		-.225*** -.297 to -.153	-.229*** -.302 to -.155	-.229*** -.303 to -.155	-.227*** -.301 to -.153
Body mass index (kg/m^2)		-.068*** -.076 to -.060	-.069*** -.077 to -.060	-.069*** -.077 to -.060	-.068*** -.077 to -.060
Diet^			.016 -.026 to .058	.016 -.026 to .058	.021 -.022 to .063
p-PTH				.00 -.019 to .019	.002 -.017 to .022
25(OH)D					.002 -.001 to .004

P<0.05*, P< 0.01**, P<0.001***, ^ Fish/shrimps as main dish, (times/week).

Paper IV

Table 11 describes the baseline characteristics of the intervention and the control groups - the groups shared similar characteristics. A comparison between the groups regarding the changes in the hormonal levels as well as ISI and DIo between the first and the third visit is provided in Table 12, both in a crude (unadjusted model) and in an extended (adjusted model). As reported earlier from the MEDIM intervention study, the levels of ISI significantly increased in the intervention group compared to the control group even after adjusting for the changes in BMI, physical activity and caloric intake using mixed models linear regression analysis [122]. Similarly, the levels of S-25(OH)D increased to a larger extent in the intervention group compared to the control group (extended model, Table 9). There were no significant differences between the groups in levels of IGF-1 and Adiponectin during follow-up (Table 12).

Table 13 shows the effect of the intervention on insulin action and secretion adjusted for changes over time in the levels of 25(OH)D, IGF-1, adiponectin, and Pro-NT respectively, adjustment is made separately for each hormone. The significant effect of the intervention remains after accounting for IGF-1, Adiponectin and Pro-NT but not after adjusting for 25(OH)D. The non-significant effect of the intervention on DIo remains even after accounting for the changes of the hormonal levels with the exception of the changes in 25(OH)D.

Table 11:
Baseline characteristics of the participants in the intervention and the control groups completing the study.

Variables	Intervention n=35	Control n=32	p-value
Age (years)	50.7 (10.2)	48.8 (8.5)	0.41
Male sex, n (%)	15 (43)	17 (53)	0.47
BMI (kg/m^2)	31.0 (4.7)	29.6 (3.6)	0.20
Mean caloric intake (kcal)	1976 (661)	2049 (646)	0.66
PA (MET*-hours/week), median	14.7	12.6	0.98
Fasting glucose (mmol/L)	5.6 (0.5)	5.4 (0.7)	0.15
HbA1$_c$ (mmol/mol)	34 (4.8)	35 (4.5)	0.64
ISI (mmol/L*mIE/L−1), median	62.5	77.4	0.11
DIo (mmol/L*mmol/L*mmol/L), median	8781	9450	0.50
Total cholesterol (mmol/L)	5.0 (0.85)	5.0 (0.95)	0.73
p-LDL (mmol/L)	3.4 (0.77)	3.5 (0.83)	0.61
p-HDL (mmol/L)	1.3 (0.33)	1.2 (0.29)	0.16
p-Triglyceride (mmol/L)	1.3 (0.5)	1.5 (0.8)	0.24
S-25(OH)D (nmol/L), median	25	20	0.70
S-IGF-1 (µg/L)	156 (48)	170 (54)	0.28
S-Adiponectin (mg/L)	8.8 (3.8)	8.7 (4.6)	0.97
Pro-NT (pmol/L)	127.5 (53.5)	118.8 (43.7)	0.48
Smoking, n (%)	6 (17.1)	5 (15.6)	1.0
Follow-up time (months)**	3.9 (0.3)	3.5 (0.4)	<0.001

Data presented as mean (standard deviation), numbers (percentages) or median. Differences between groups were compared using independent sample t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed continuous variables. Chi-square test for categorical variables. PA=physical activity, * Metabolic equivalent of task.

Table 12:
Change over time in the levels of 25(OH)D, IGF-1, Adiponectin, ISI and DIo (log_e-transformed) in the intervention group compared to the control group. The β is a parameter estimate for the interaction term "group-status" x "time since baseline visit (months)".

Outcomes	Crude model (n=65)			Extended Model + (n=65)		
	β	p-value	Confidence interval	β	p-value	Confidence interval
DIo (mmol/L*mmol/L*mmol/L)	0.030	0.557	-0.074 to 0.132	0.076	0.250	-0.055 to 0.207
ISI (mmol/L*mIE/L−1)	0.099	0.007	0.028 to 0.171	0.115	0.013	0.025 to 0.204
S-25(OH)D (nmol/L)	-0.012	0.584	-0.055 to 0.031	0.061	0.023	0.009 to 0.113
S-IGF-1 (µg/L)	-0.006	0.773	-0.044 to 0.033	0.043	0.129	-0.013 to 0.1
S-Adiponectin (mg/L)	0.006	0.695	-0.025 to 0.037	-0.013	0.508	-0.054 to 0.027
Pro-NT (pmol/L)	11.60	<0.001	5.39-17.81	12.92	0.002	4.69 to 21.15

The analysis included all individuals with data available for at least two time points. The β-coefficient percentage change (calculated as 100*(exp β-1) in the outcomes per month in the intervention group compared to the control group. + Adjusted for BMI, physical activity (Metabolic Equivalent of Task) and caloric intake.

Table 13:
The effect of the intervention on ISI and DIo (loge-transformed) after accounting separately for 25(OH)D, IGF-1, Adiponectin and Pro-NT respectively. Data adjusted for BMI, physical activity and caloric intake, in the intervention group compared to the control group. The β is a parameter estimate for the interaction term "group-status" x "time since baseline visit (months)".

	ISI as dependent variable			DIo as dependent variable		
Variable	β	p-value	Confidence interval	β	p-value	Confidence interval
S-25(OH)D (nmol/L)	0.129	0.078	-0.016 to 0.274	0.215	0.008	0.064 to 0.366
S-IGF-1 (µg/L)	0.119	0.050	-0.001 to 0.239	0.128	0.069	-0.011 to 0.267
S-Adiponectin (mg/L)	0.124	0.040	0.006 to 0.242	0.124	0.078	-0.154 to 0.264
Pro-NT (pmol/L)	0.109	0.032	0.001 to 0.207	0.113	0.106	-0.025 to 0.250

The analysis included all individuals with data available for visit one and three. The β-coefficient percentage change (calculated as 100*(exp β-1) in the outcomes per month in the intervention group compared to the control group.

Discussion

Ethnic differences in insulin action and secretion

In the first study of this thesis, we reported that both insulin action (represented by ISI) and β-cell function (represented by Dio), decline with increasing age in the Iraqi and Swedish-born cohorts. The Iraqi immigrants suffer from insulin resistance at earlier ages as the median level of ISI among the youngest Iraqi-born immigrants (< 39 years of age), was even lower than that of the oldest Swedish-born participants. The Iraqi immigrant population displayed lower median levels of ISI in all age groups compared to the Swedish population even after adjusting for factors such as BMI and family history of T2D. Furthermore, the insulin secretion level represented by DIo observed in the young Iraqis (<39 years) is seen among the 7-9 years older Swedes. β-cell dysfunction contributes to the development of T2D and appears in high-risk individuals years before the onset of T2D. As illustrated earlier by the MEDIM cohort reports, the Iraqi-born individuals develop T2D about a decade earlier than their Swedish counterparts [32, 147-150].

BMI is the main risk factor for T2D pandemics in the MENA region [151-153] and in this study we confirm that BMI has a great impact on glucose regulation, including insulin sensitivity and action and being. The high susceptibility among ME individuals to T2D with early onset and early decline in the insulin secreting capacity could indicate a genetic variant burden, influencing insulin secretion. Early data from the MEDIM cohort suggests a strong association between insulin secretion, T2D and family history of diabetes [154]. T2D is increasing among non-obese Asians, with a prevalence of T2D among non-obese individuals as high as 60-80% in some Asian countries, suggesting genetic inheritance of insulin resistance [155-157]. Inherited defect in β-cell compensation prior to the onset of T2D is one of the suggested factors predisposing non-obese ME individuals to T2D [158-162].

It has been shown previously that genetic risk variants for T2D are more strongly associated with defective insulin secretion [148, 163, 164]. It is a question for future research to address how early the declines in insulin action and secretion start in a ME population.

Ethnic differences in ACM, cancer, CVD and CSM

In the second study of this thesis, in an 8-year follow-up, we showed that the ACM, CVD, cancer incidence and CSM were lower in the Iraqi-born group compared to native-born Swedes. This is despite the heavy burden of cardiometabolic risk factors among the Iraqi-born MEDIM population, such as obesity, insulin resistance, physical inactivity and T2D, and hence constitutes a paradox.

Immigrants compared to native populations have been shown to have a survival advantage and lower incidence of cancer disease and cancer mortality compared to native populations [43, 165, 166]. The lower mortality rates among immigrants and especially non-European immigrants have been reported not only in healthy populations but also in a Swedish observational cohort study of 62,557 individuals with hypertension and with and without diabetes [42] as well in nationwide data of individuals with new-onset T2D in Sweden, showing lower mortality rates among first-generation immigrants with T2D [40]. This study does not only confirm earlier observations, but it also provides unique data on anthropometrics and lifestyle behaviours providing adjusted data rather than only register observations. The Iraqi-born participants in the MEDIM cohort did not only have a higher prevalence of metabolic risk factors but also a higher prevalence of mental health problems such as anxiety and depression [167]. The fact that the mortality rates of second-generation immigrants merge with that of the host population suggests possible gene-environment interactions may occur due to adaptation to Western lifestyles [40]. To examine CSM differences between immigrants and US-born individuals, data from the National Longitudinal Mortality Study were analysed taking into account socioeconomic, occupational, and demographic factors. Lower ACM and CSM mortality rates were reported for immigrants compared to US-born [43]. About 300,000 adults were included in the study and the CSM studied were death from CVD and cancer disease [43]. In a population-based register study from Sweden, 10 million individuals aged 20 years or older were followed between 1992 and 2016. The HR of all-site cancer was slightly lower among immigrants compared to native Swedes except for infection-related cancer diseases [168].

There are few studies comparing the incidence of cancer among immigrants from the ME compared to endogenous populations. The studies available show diverse results with higher incidence among Arabs for some cancer types such as thyroid cancer and lower for other types such as lung and prostate cancer [169, 170]. As for immigrants to Sweden, a register study of the Swedish Family-Cancer Database (1958-1998) addressing cancer risk in first-generation immigrants has shown that cancer incidence varies greatly, with the lowest cancer incidence found among Iraqi men and Arab women [66].

Studies on CVD incidence and mortality among migrant populations compared to host populations have shown that with longer duration of residence in the host

countries, migrants have similar or higher rates of CVD compared to those of the host populations [171]. A systematic review of publications between 2000 and 2014 addressing the risk of CVD among immigrants to high-income countries showed that ME migrants in Western Europe had similar or higher rates of CVD than the host populations [172]. Our findings of lower rates of CVD among Iraqi immigrants compared to the native Swedish control group could be explained by a shorter follow-up time.

Studies of longer duration and studies of second-generation immigrants are needed to understand the changes over time in the incidence and mortality rates of cancer and CVD as well as ACM. Longer duration studies are needed to understand whether the lower incidence rates and the survival advantage reported in this paper remain with longer duration of stay in the host country or converge towards the rates of the native population.

Ethnic aspects on Vitamin D insufficiency and deficiency

The third study in this thesis reports that the lower levels of insulin action in Iraqi immigrants could be explained by Vitamin D deficiency. In this study, the differences in the levels of 25(OH)D and PTH between the Iraqi-born immigrants and the Swedish-born remained significant after adjusting for the confounding effect of factors potentially influencing Vitamin D and PTH, such as physical activity and the intake of fish and shrimps as main dishes. Several large epidemiological studies such as The Longitudinal Aging Study Amsterdam [173], the 1958 British Birth Cohort [173] and the Nurse's Health Study [174], have found 25(OH)D deficiency to be associated with higher fasting glucose, insulin resistance and higher relative risk for T2D [87]. The MEDIM cohort reported the Iraqi participants to have similar risk factors associated with Vitamin D deficiency [32]. The MEDIM study also reported ethnic differences in insulin action and, in this MEDIM cohort, we see these differences diminish after adjusting for the confounding effect of Vitamin D. Ethnic differences in insulin sensitivity associated with 25(OH)D levels have been reported in other cross-sectional studies [175, 176]. A meta-analysis, including 18 RCTs and 20 observational studies with 1243 and 11,063 participants with diabetes, showed significantly higher insulin sensitivity among participants with vitamin D supplementation [177-179]. In our study, we did not see any association between the levels of 25(OH)D and insulin secretion. Studies showing this association suggest that Vitamin D exerts a positive effect on insulin secretion only when calcium levels are adequate and in this study we cannot adjust for calcium levels to confirm the association since calcium was not analysed in the cohort [180]. 25(OH)D insufficiency/deficiency is more common in non-Western

immigrants to Europe [94, 181, 182] and the prevalence of vitamin D insufficiency in the MENA region ranges between 44-96% in adults and 12-96% in children when comparing the results from 41 observational studies from the MENA region [91]. In a recent Swedish study immigrants of ME descent had almost seven times higher odds of having inadequate 25(OH)D levels, defined as 25(OH)D levels below 50 nmol/L [183]. The participants were free from T2D but there was a trend towards higher fasting blood sugar among individuals of ME ancestry. The participants were all recruited when seeking medical attention in primary health units and as such are not a representative sample of a healthy migrant group. The participants were not asked to provide information about dietary habits and physical activity which was a limitation of this study. Plausible contributing factors to the highly prevalent 25(OH)D deficiency in non-western immigrants are the differences in skin pigmentation and the modest clothing among ME immigrants due to religious causes or cultural habits [184]. However, in Paper III we do not see differences in the levels of 25(OH)D when comparing Iraqi females to males despite the Iraqi males having a more Westernised dress code. Lack of dairy products in the ME diet [185] and the excessive sunshine in the countries of origin hence making people avoid sun exposure are other factors suggesting the lower 25(OH)D in ME populations [184].

In a nationwide Swedish study (n = 2,775,736) [186], a generally lower risk for osteoporotic fractures in first-generation immigrants was observed with an exception for Iraqi men who had a higher osteoporotic fracture risk. Among the second-generation immigrants to Sweden, the osteoporotic fracture risk was similar to Swedish natives [187]. Thus, it is still unclear if the levels of 25(OH)D, considered "adequate" for bone and mineral metabolism in a ME population are the same as in a European population. This study emphasises the potential advantages of having sufficient 25(OH)D levels, especially in a population at high risk for metabolic disturbances associated with 25(OH)D deficiency.

Lifestyle intervention and hormonal changes

In the fourth study of this thesis, we studied a cohort of Iraqi participants at high risk of developing T2D. Our results show that the effect of the culturally adapted lifestyle intervention on insulin action represented by ISI and insulin secretion represented by DIo is associated with changes in the levels of 25(OH)D. The levels of 25(OH)D were significantly higher in the intervention group by visit three after adjusting for changes in BMI, physical activity and caloric intake. Vitamin D is suggested to be involved in both insulin action and secretion due to the presence of VDRs on the human pancreatic β-cells [88], and the presence of a vitamin D response element in the human insulin gene promoter [90]. Several studies have demonstrated an association between vitamin D insufficiency and insulin resistance

in ME populations in Western countries [181, 188]. However, studies have shown inconsistent results regarding the effect of Vitamin D supplementation on insulin sensitivity and insulin secretion [189-194]. Our findings are consistent with earlier studies indicating that lifestyle intervention can have a positive effect on the levels of 25(OH)D [195].

Our study shows no significant differences in the levels of IGF-1 but a trend towards higher levels of IGF-1 in both the intervention and the control group at the third study visit. The association between BMI and IGF-1 is more complicated since both high and low IGF-1 levels are associated with a higher risk of obesity, insulin resistance and T2D [73, 101]. IGF-1 levels have been shown to increase in 12 months follow-up post bariatric surgery and increased physical activity has also been shown to increase IGF- levels [196, 197]. In a similar manner, weight loss due to bariatric surgery has a positive effect on adiponectin levels as well as lower BMI [198]. Even if produced in the adipose tissue, adiponectin is higher in lean subjects due to the inhibiting inflammatory effect associated with obesity [199]. Even here our study shows a trend toward higher levels of adiponectin in both groups but with no significant change in the adiponectin concentration in the intervention group compared to the control group. Pro-NT levels significantly increased in the intervention group and this has been reported earlier by Bennet et al. [200] suggesting that lifestyle interventions might affect the satiety mechanism mediated by NTR1 [200, 201]. Another explanation for the increase of Pro-NT is a compensatory mechanism in order to restrain body weight such as seen in the higher levels of Pro-NT post bariatric surgery [202].

In this paper, we could not show a significant effect on ISI and DIo after adjusting for IGF-1, Adiponectin and Pro-NT. Obesity and T2D are conditions associated with chronic inflammation which in turn affects the levels of the above-mentioned hormones. Larger intervention studies of longer duration are needed in order to fully understand the effect of extra pancreatic hormones on insulin metabolism.

Strengths and Limitations

Study I: A strength is the large well-phenotyped cohort, with a representative study sample. Oral glucose tolerance tests were assessed, and Matsuda indices were used with good reliability and correlation to euglycemic insulin clamp. The Matsuda indices reflect both hepatic and muscular insulin sensitivity.

Increasing age was a proxy for change over time. A limitation of the study is that Iraqi men participated to a higher degree compared to Iraqi women. Another limitation is the cross-sectional design where individuals were not followed over time, and potential confounding risk factors could have existed much earlier at birth or early childhood. Thus, causality could not be studied.

Study II: Data from the MEDIM cohort are collected through health examinations, questionnaires, fasting samples and OGTT, all conducted by trained bilingual nurses (Arabic, English and Swedish). The method of collecting the data has allowed for relevant and specific adjustments providing more accurate conclusions of the register-based outcomes.

A potential limitation is the fact the Iraqi participants were younger than the Swedish control group. Despite adjusting for age, this could have underestimated the rate of some cancer diseases. Another limitation is the relatively short follow-up time and the fact that we studied all types of cancer as one unit (due to the small number of cases).

Study III: In this study, the differences in the levels of 25(OH)D and PTH are adjusted to anthropometrical measures such as age, sex, dietary, lifestyle habits as well as glucose metabolism allowing more accurate comparisons between the groups. Blood samples from both groups were collected during the same time frame, and the association between insulin action and secretion to the levels of 25(OH)D and PTH are all unique to this study. Another strength is the fact the earlier results from the MEDIM cohort have shown ethnic differences in insulin action and how these results are altered after adjustment is made to 25(OH)D. In this study, we can show that the levels of 25(OH)D do not differ between Iraqi males and females, despite the modest clothing of most Arab females.

A weakness of the study is the lack of information regarding calcium levels. Another weakness is the lack of information regarding sun exposure habits.

Study IV: This study is unique in studying other hormonal factors potentially involved in glucose metabolism and inspires future research of larger samples and longer duration to better understand the hormonal changes and the effect on insulin action and secretion.

The limitations are the small study sample and the shorter duration of follow-up due to the high dropout rate and the occurrence of the month of Ramadan when many Muslims choose to fast for longer hours.

Conclusions

Paper I

Ethnic differences across ethnicities regarding insulin secretion and action with Iraqi immigrants show a decrease in insulin secretion over time as well as lower insulin sensitivity as compared to Swedes at early ages. The differences in insulin secretion seem to be related to the Iraqis having higher BMI compared to Swedes. Over the age span considered the changes in insulin secretion and insulin action appear similar regardless of ancestry. The early decline in insulin action and secretion explains the early T2D onset among the Iraqi population.

Paper II

Iraqi-born immigrants have lower ACM rates than Swedish-born as well as lower rates of cancer, CVD, and CSM. The differences in mortality and cancer rates across European and Middle Eastern ethnicities are not fully explained by age, sex, anthropometrical measures, glucose regulation and lifestyle but lie elsewhere. This is rather a paradox considering the higher risk for T2D and obesity observed in ME immigrants.

Paper III

Significant differences in the levels of Vitamin D and PTH between the Iraqi-born immigrants and the Swedish-born natives with Iraqis having lower levels of Vitamin D and higher levels of PTH. The ethnic differences in insulin action previously found between Iraqi-born and native-born Swedes could be explained by differences in 25(OH)D levels.

Paper IV

A four-month culturally adapted lifestyle intervention program on Iraqi-born individuals at high risk of developing T2D increases the levels of 25(OH)D. The effect of lifestyle intervention on insulin action and secretion is altered when adjusting for 25(OH)D.

Clinical Implications

Considering the high proportion of Middle Eastern immigrants who are at risk of developing type 2 diabetes, a great cost will be imposed on healthcare and society because of loss of productivity years and life-years. A proper understanding of contributing risk factors across ethnicities is required to tailor preventive actions and treatment of this population. Our studies raise awareness among clinicians on how early the decline in insulin action and secretion is noticed in the Iraqi group. With this work we also shed light on Vitamin D as an important factor in metabolic syndrome and the majority of Iraqis have Vitamin D levels below the recommended levels. We wish to raise awareness among clinicians regarding the known and potential advantages of having sufficient 25(OH)D levels.

Future research

Long-term follow-up studies are needed to better understand the pathophysiological processes affecting insulin action and secretion in ME populations. Studies are also needed to understand if the lower insulin action and sensitivity are processes decided by genetic factors starting in childhood or appear later in life and at which ages.

In our second study, we show survival advantage and lower incidence of cancer, CVD, and CSM among Iraq-born immigrants in an eight-year follow-up. Longer duration follow-up studies of first-generation immigrants are needed to better understand if the survival rates and disease incidence rates merge with the host populations.

Moreover, the genetic, epigenetic, environmental, or hormonal factors contributing to survival advantage as well as lower incidence of cancer, CVD, and CSM among ME immigrants need to be identified in future studies.

The MEDIM culturally adapted interventional study considered cultural barriers which restricted the attempts to lifestyle improvements especially among ME females. Future trials are encouraged to take cultural aspects into account. Future interventional studies are also needed to evaluate the effect of Vitamin D supplementation on insulin action and secretion, comparing ME immigrants and native Europeans. The aim of interventional trials will be to improve T2D prevention and enhance glucose regulation.

Populärvetenskaplig sammanfattning

Bakgrund

Typ 2 Diabetes (T2D) är en kronisk och allvarlig sjukdom som drabbar allt fler människor i hela världen. Globala sjukdomsbördan skiljer sig beroende på vilken världsdel man kommer ifrån, Mellanöstern och Nord Afrika är områden som är hårt drabbade med väldigt hög förekomst av T2D. Riskfaktorer för T2D är övervikt särskilt bukfetma, minskad insulinkänslighet eller insulinresistens och låg grad av fysisk aktivitet. I Sverige är det ungefär 4–5% av den vuxna befolkningen som har en diabetesdiagnos och majoriteten har T2D. Migration och urbanisering ger ökad risk för T2D och diagnosen förekommer i högre grad bland invandrare från Mellanöstern. 20% av Sverige befolkning utgörs av individer födda utanför Sverige och individer födda i Mellanöstern utgör största invandrargrupperna i Sverige.

År 2010 startades MEDIM studien, MEDIM är akronym för betydelsen av migration och etnicitet för diabetes i Malmö. Till MEDIM rekryterades ca 2000 invånare i Malmö mellan 30–75 år gamla födda i Irak eller i Sverige och deltagarna genomgick hälsoundersökningar, lämnade blodprover och fyllde i olika frågeformulär om livsstil och sjukdomshistoria. Resultaten från MEDIM visade att individer födda i Irak har dubbelt så hög förekomst av T2D jämfört med svenskar och att irakier har även hög ärftlighet för T2D.

T2D är en komplicerad sjukdom som orsakas av en kombination av nedsatt insulinkänslighet i kroppens olika celler och minskad insulinproduktion från bukspottkörteln. T2D ger ökad risk för komplikationer i form av tidig död, hjärt- och kärlsjukdomar samt cancersjukdomar.

Brist på Vitamin D är vanligt förekommande bland individer från Mellanöstern och tidigare forskning har visat att det finns en koppling mellan brist på vitamin D samt övervikt, insulinresistens och T2D.

Syftena med denna avhandling var att undersöka hur insulinproduktion och känslighet påverkas med åldrande och hur dessa processer skiljer sig bland irakier och svenskar i MEDIM studien. I denna avhandling har vi också haft för syfte att studera etniska skillnader i dödlighet, förekomst av hjärtkärlsjukdomar och cancersjukdomar samt hur dödligheten i dessa sjukdomar skiljer sig bland irakier och svenskar från MEDIM studien.

Tredje syftet har varit att undersöka skillnader i Vitamin D nivåer samt om dessa skillnader påverkar graden av insulinproduktion och känslighet hos irakier i jämförelse med svenskar från MEDIM Studien.

Sist har vi haft för syfte att undersöka hur en livsstilintervention i form av minskat kaloriintag och ökad fysiskaktivitet hos irakier med hög kroppsvikt och nedsatt insulinkänslighet utan diabetesdiagnos påverkar insulinkänsligheten och om denna påverkan beror på nivåerna av Vitamin D och andra hormoner som tros vara kopplade i kolhydratmetabolismen.

Metod

Studiepopulationen i denna avhandling kommer från MEDIM studien som rekryterade irakfödda individer i Malmö och en svenskfödd kontrollgrupp från samma områden i Malmö mellan år 2010–2012. Individerna gav sitt informerade samtycke till att delta i studien och alla förutom de med en T2D diagnos fick genomgå sockerbelastningar. Deltagarna fick dricka en sockerlösning och lämna blodprover vid olika tidpunkter för att undersöka blodsocker- och insulinnivåerna. Individer fyllde i frågeformulär om matvanor, fysiskaktivitet, rökvanor, alkoholkonsumtion, medicinintag, tidigare eller pågående insjuknanden i hjärtkärlsjukdom och cancer samt ärftlighet för T2D. Information om dödlighet, nya fall av hjärtkärl- och cancersjukdomar hos deltagarna hämtades från registerdata under 8 år från deltagande i MEDIM, dvs. fram till 2018. Vitamin D prover analyserades i cirka hälften av MEDIM populationen. Av de irakiska deltagarna fick de med hög risk att utveckla T2D ett erbjudande om att delta i en livsstilsinterventionsstudie. De som tackade ja till deltagande lottades in i en interventionsgrupp som fick tillgång till gruppträffar, matlagningsträffar, gymkort och råd om hälsosamma vanor samt information om T2D och förebyggande åtgärder. Kontrollgruppen fick sedvanlig skriftlig och muntlig information som man brukar få inom dagens sjukvård.

Resultat

Insulinkänslighet och insulinproduktion avtar med stigande ålder och detta noterades hos både irakier och svenskar. Irakier hade både lägre insulinkänslighet och lägre insulinproduktion jämfört med svenskar och skillnader i insulinkänslighet kunde inte förklaras av faktorer som övervikt, ålder, kön och graden av fysiskaktivitet.

Irakier hade lägre dödlighet och lägre risk att insjukna i hjärtkärl- samt cancersjukdomar jämfört med svenskar trots den ökade förekomsten av T2D.

Irakier hade mycket lägre nivåer av Vitamin D jämfört med svenskar och livsstilsintervention hos irakier resulterade efter 4 månader i högre insulinkänslighet

samt högre nivåer av Vitamin D. De låga Vitamin D nivåerna hos de irakiska deltagarna kan åtminstone delvis förklara de lägre nivåerna av insulinkänslighet.

Slutsatser

Det finns skillnader i graden av insulinkänslighet mellan Irakiskfödda och Svenskfödda. Orsakerna till det kan möjligen förklaras av genetiska faktorer eller vara relaterade till D-vitaminbrist. Dessa orsaker är i behov av att studeras vidare med uppföljningsstudier. Överlevnadsfördelen hos irakierna är en paradox som måste studeras med uppföljningsstudier av längre duration för att undersöka närmare om skillnaderna mellan irakier och svenskar gällande dödlighet, hjärtkärl- och cancerinsjuknande jämnar ut sig med längre tids vistelse i Sverige samt studera närmare de skyddande faktorerna som förekommer hos den irakiska gruppen.

Vitamin D brist förekommer i högre grad hos individer med ursprung i Mellanöstern utan skillnader mellan könen. De irakiska männen som inte bär på heltäckande klädsel har lika mycket brist jämfört med de irakiska kvinnorna och klädseln verkar inte förklara de stora skillnaderna i Vitamin D nivåer mellan irakier och svenskar. Vidare forskning behövs för att adressera orsakerna till de stora skillnaderna och Vitamin D:s betydelse i utvecklande av T2D.

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