

# Type 2 diabetes in migrants: register-based analyses

PhD dissertation

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# Preface

## Motivation

During my work as a junior doctor in a general practice in Gellerup, a deprived suburb of Aarhus with a large migrant population, I was immediately struck by the high frequency of type 2 diabetes (T2D) and other chronic diseases among day-to-day consultations. I would quickly learn that T2D held more surprises for me than just a high prevalence, and after just a few weeks it seemed that much of what I had learned about the disease in medical school and studied in clinical guidelines did not apply in my new setting. Patients were not only more prevalent, they were also much younger, and hemoglobin-A1c (HbA1c) levels rarely came close to guideline targets despite our best efforts to intensify treatment. Sadly, these experiences would repeat themselves in my subsequent work with migrants as a general practitioner (GP) in health clinics of the Danish Red Cross at asylum residence centers and pre-removal detention centers.

As I reviewed the literature, I understood why medical school and guidelines had failed to prepare me for the challenges I faced as a clinician with T2D in migrants: the existing literature was inadequate. While increased prevalence of T2D appeared well-established, and migrants with T2D were also ascribed a higher mortality than their native counterparts, this provided little guidance for my day-to-day work. Contrarily, there was hardly any evidence on disparities in the time between diagnosis and death - the time when care from the GP is needed the most. So I was left to wonder what might cause this discordance between what I knew about T2D from books and guidelines, and what I encountered in migrants in the clinic.

*Are migrants with T2D more prone to under-treatment, and in which areas of care?*

*Are some migrant groups more prone to under-treatment than others?*

*Are their needs for T2D care simply greater?*

Knowledge on these clinical questions would enable GPs and healthcare planners to address disparities and improve care in migrants by prioritizing and focusing care accordingly. Migrants are currently a younger demographic than the rest of the population, but as time causes the migrant demographic to age, it is likely that migrants will constitute an increasing proportion of the T2D population in the coming years. Therefore, I was excited to explore these urgent clinical questions as a researcher, hoping I could provide

answers to myself and fellow GPs that could lead to better care - and, ultimately, better health - in a vulnerable and challenging group of patients.

During my time as a PhD student, I quickly encountered the first of many challenges on the way to studying migrants with T2D in the Danish registers: there was no validated definition of T2D, nor a common consensus among researchers. This led to the PhD project expanding its scope to develop and validate a tool to define T2D in the Danish registers, which allowed me to answer my research questions based on robust findings. This PhD project benefited greatly from open-source tools, and in the spirit of open science, the source code of the validated diabetes classifier was made available to other researchers in the *osdc* package for the *R* statistical programming language. As a final commitment to openness, this dissertation was made available to a global audience in website format at [aastedet.github.io/dissertation/](https://aastedet.github.io/dissertation/).

## Outline of the dissertation

**Chapter 1** introduces type 2 diabetes (T2D) and the special risk it poses to migrants. It then describes the context of T2D care in Denmark and summarizes clinical guideline recommendations and how they relate migrants with T2D. Finally, it introduces the reader to identification of diabetes patients in Danish healthcare registers.

**Chapter 2** states the overall aims of this PhD project and each individual study.

**Chapter 3** describes the setting, data sources, methods and study designs used in the studies of this PhD project.

**Chapter 4** presents the main results of the studies.

**Chapter 5** contains a discussion of the methods used and their potential impact on results.

**Chapter 6** discusses the findings in light of the methods used.

**Chapter 7** presents the main conclusions and their clinical implications.

**Chapter 8** draws up future perspectives of the PhD study and research field.

## **Papers associated with the dissertation**

Coming soon



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## Abbreviations

**ACEI:** Angiotensin-converting enzyme-inhibitors  
**ARB:** Angiotensin receptor blockers  
**CVD:** Cardiovascular disease  
**DKD:** Diabetic kidney disease  
**GP:** General practitioner  
**GDM:** Gestational diabetes mellitus  
**GLD:** Glucose-lowering drugs  
**HbA1c:** Hemoglobin-A1c  
**LDL-C:** low-density lipoprotein cholesterol  
**LLD:** Lipid-lowering drugs  
**T1D:** Type 1 diabetes mellitus  
**T2D:** Type 2 diabetes mellitus  
**UACR:** Urine albumin-to-creatinine ratio

# 1. Introduction

*[This paragraph should introduce the overall context, and very briefly introduce the aims/niche of the project: Why did I do this?]*

This chapter describes type 2 diabetes (T2D) and how migrants are at particular risk. It also describes the context of care in Denmark and summarizes clinical guideline recommendations and how they relate to the needs of migrants with T2D. Finally, it introduces the reader to identification of diabetes patients in Danish healthcare registers as a means to provide much-needed knowledge on potential disparities in T2D care between migrants and native Danes.

## 1.1. Migrants and type 2 diabetes

T2D constitutes the vast majority of all diabetes cases, and disproportionally affects the socially deprived demographics in societies across the globe[manglerref]. The prevalence of type 2 diabetes (T2D) today exceeds half a *billion* people globally and is on the rise due to several factors, including population aging, urbanization, adoption of energy-dense diets, and sedentary lifestyles. These transitions are occurring at a rapid pace in developing countries, where they affect the largest number of people<sup>1</sup>. Many developing countries have populations with a genetic predisposition to developing T2D, which exacerbates the impact of these transitions.

Migrants are particularly vulnerable to T2D, as they are positioned at the point of convergence of these exposures: genetic predisposition, rapid lifestyle transitions, and the disparate social impact of T2D. After being granted residence permit in Denmark and other developed nations, migrants are often housed in densely-populated urban areas and exposed to drastic lifestyle transitions. Migrants may also suffer from previous mental and physical trauma, which - in addition to cultural and language barriers - can limit their ability to gain higher-income employment and escape their disadvantageous socioeconomic position.

In Denmark and many other developed nations, healthcare systems are facing a challenge to sustain the expected high quality of care in an aging population with a growing burden of chronic diseases and comorbidities. Prioritization of limited resources is crucial to

ensure that those with the highest need for (and potential benefit from) healthcare receive adequate care. Migrant origin is a well-established risk factor of T2D, and migrants have a higher prevalence of T2D compared to native populations today[manglerref], but the increased risk of developing T2D is partially mitigated by their younger age. However, this only delays the impact of their increased T2D risk, and as these migrant populations age in the coming years, they will make up a growing proportion of T2D patients in the country - 9% of immigrants in Denmark were aged 66 years and above in 2019, a proportion projected to double by 2039<sup>2</sup>. Therefore, understanding potential disparities in care and the specific healthcare needs of migrant populations with T2D can inform the prioritization of healthcare resources, ultimately ensuring that all individuals with T2D can continue to receive appropriate care.

Currently, there is a lack of evidence on T2D care in migrants, and research in this area faces several challenges that may explain the scarcity of evidence. Not only are migrants a minority, which limits the size of potential study populations, they are often a hard-to-reach group in studies that require patient engagement for inclusion, which exacerbates sample size problems and can induce selection bias in such study designs. Furthermore, migrants have historically been defined by their racial appearance and ethnic minorities categorized accordingly, particularly in Europe and the United States. While these categories allow researchers to identify racial minorities, they obscure the role of migrants in the modern era, and provide only indirect evidence on migrant minority groups<sup>3</sup>.

## 1.2. Migrants in Denmark

In 2019, Denmark had a population of approximately 5.8 million residents, of whom 600.000 (10%) were migrants and 1 million (18%) were aged 66 years and older. By 2039, the population is expected to have grown to 6.2 million, with a migrant population of 750.000 (12%) and 1.5 million individuals (23%) aged 66 years and older.<sup>2</sup> Figure 1.1 shows the projected demographics of native Danes and migrants.

### 1.2.1. Migration

Individuals migrate between countries for various reasons, such as the pursuit of work, education and family reunification, or to seek protection. Due to different international rights, a clear legal distinction is made between ‘refugees’ and ‘migrants’. Refugees are defined by the United Nations High Commissioner for Refugees, and protected in accordance with international law:



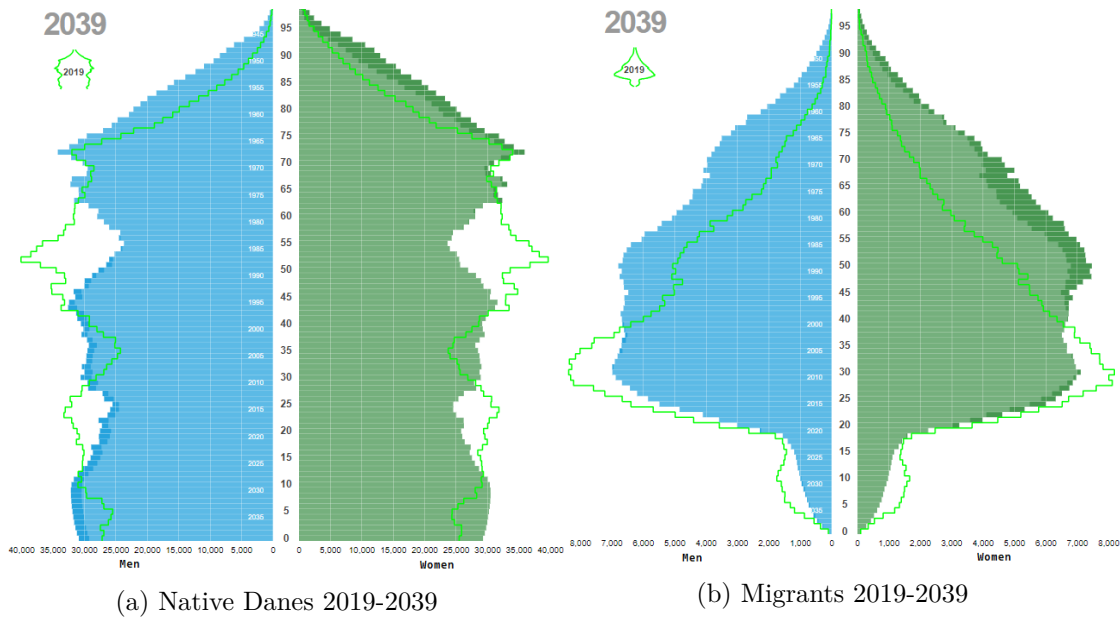


Figure 1.1.: Demographic projections of native Danes (a) and migrants (b) in 2039. Demographics in 2019 are outlined in green. Adapted from Statistics Denmark<sup>2</sup>

Refugees are persons who are outside their country of origin for reasons of feared persecution, conflict, generalized violence, or other circumstances that have seriously disturbed public order and, as a result, require international protection.<sup>4</sup>

By contrast, there is no formal legal definition of an international migrant, although anyone changing country of usual residence, irrespective of the reason for migration or legal status, is generally considered a migrant.<sup>4</sup>

In Denmark, migrants seeking protection are processed by authorities to determine if they qualify for refugee status, and whether they have previously applied for asylum elsewhere in the European Union per the Dublin Regulation.<sup>5</sup> Individuals qualifying for refugee status are granted asylum and receive residence permits. Conversely, individuals with immediate family members holding Danish citizenship (or with residence permit granted for reasons other than refugee status) can apply for a residence permit on grounds of family reunification before entering the country,<sup>6</sup> and residence permits can also be granted to citizens of the European Union, as well as individuals with work or study obligations in Denmark.<sup>7,8</sup> Citizens of Finland, Iceland, Norway and Sweden are free to enter, reside and work in Denmark.<sup>9</sup>

Once residence has been granted, regardless of the reason, these individuals have access

to the same public healthcare services as Danish citizens.

### 1.2.2. Migrants in the Danish data infrastructure

In the context of Danish registers and this PhD project, both refugees and immigrants are referred to as migrants after obtaining residence. In contrast to the automated collection of data on events occurring in Denmark, migrants and their past pose a challenge to register data collection.

Basic civil registration data on migrants is collected during processing of residence applications. Generally, registrations pertaining to events that occurred in another country prior to immigration require technical evidence (e.g. clinical imaging to determine age and verify date of birth) or legal proof from the issuing authority of the country where the event occurred. However, in cases where such documentation is unavailable, registrations may be supported by undocumented information provided by the migrant.<sup>10</sup> In cases where information was not systematically collected at the time of migration, e.g. an individual's level of education attained before migration, surveys have been used to collect this data retrospectively, or it may be imputed based on available data.<sup>11</sup>

### 1.2.3. Migrant groups in Denmark

In Danish civil register data, a migrant's country of origin is defined by Statistics Denmark according to the following rules (paraphrased):

An immigrant is a person born abroad to non-Danish citizens. If Danish civil records contain data on a migrant's mother, country of origin is defined by the mother's country of birth. Otherwise the father's country of birth is used, or - if no data is available - country of origin is defined by the country of birth of the immigrant themselves.<sup>12</sup>

Migrants from more than 200 different countries of origin reside in Denmark, making the migrant group very heterogenous with respect to geographic and cultural background.<sup>12</sup> Furthermore, the context of migration differs greatly between migrants of different origins in terms of when and why a particular minority migrated to Denmark. For example, the vast majority of migrants from Turkey were granted residence due to work and family reunification in the 1960s and 1970s, while almost all migrants from Bosnia-Herzegovina were refugees from the Yugoslav wars of the 1990s. Migrants from other European countries reside in Denmark mainly for work, education or other reasons and came at various points in time. Figure 1.2 shows the primary reason for migration among the

largest migrant origin groups residing in Denmark, while Figure 1.3 shows the calendar year of immigration in different migrant groups.

The limited size of each ethnic minority and the strongly contrasting characteristics between them poses a challenge to statistical processing. Researchers must strike a balance between aggregation to achieve adequate sample sizes while preserving clinically meaningful minority groups, and avoid introducing biases due to aggregation of dissimilar groups.<sup>14</sup> For statistical purposes, different geoschemes have been used by different institutions depending on the context and purpose. The Statistical Division of the United Nations developed the *M49 Standard Country or Area Codes for Statistical Use*,<sup>15</sup> while Statistics Denmark group migrants into Western and Non-western countries, respectively, a grouping that resembles the more widely-used classification of developed and developing countries.<sup>16</sup> See Chapter 3 for a description of grouping of countries of origin in the context of this PhD project.

#### 1.2.4. Descendants

Descendants of migrants pose an additional challenge to classification for research purposes, as they can be considered part of the migrant group, the native population, or their own distinct demographic. In the context of T2D today, descendants of migrants in Denmark are a very young demographic unlikely to constitute a substantial proportion of the patient population (less than 1% of descendants are aged 66 years or older).<sup>2</sup> There is also some evidence from Sweden suggesting that descendants are a distinct group from first-generation immigrants in terms of T2D and mortality.<sup>17</sup> In the context of this PhD project, descendants were not a focus of investigation, and the term migrants specifically refers to first-generation migrants.

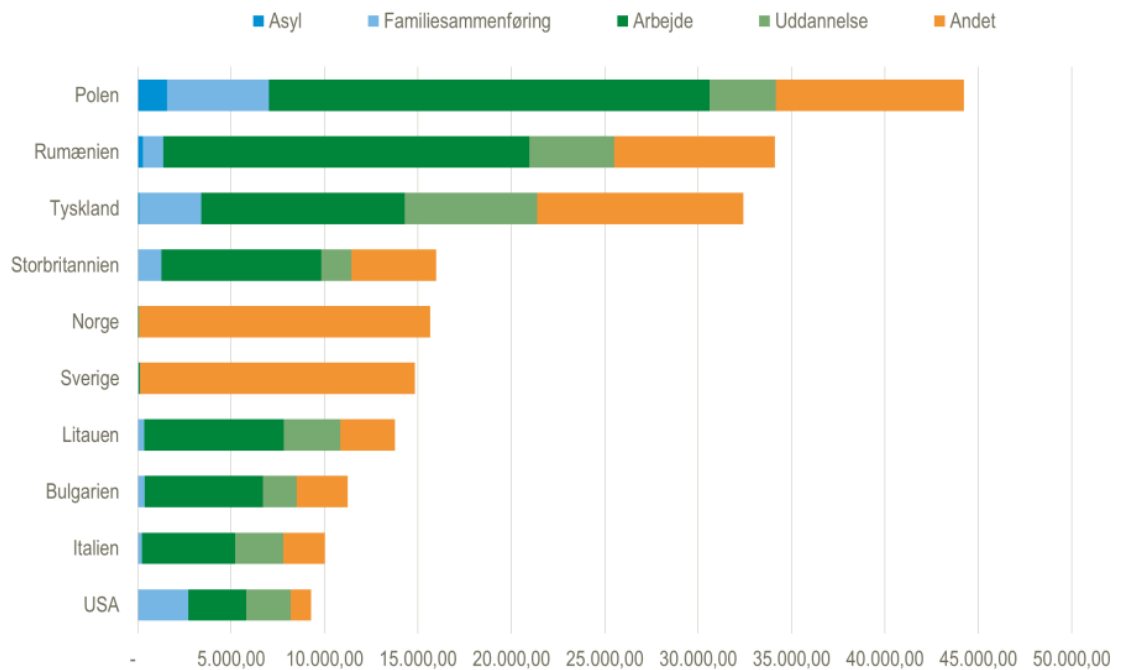
## 1.3. Type 2 diabetes care

### 1.3.1. Complications and risk factors

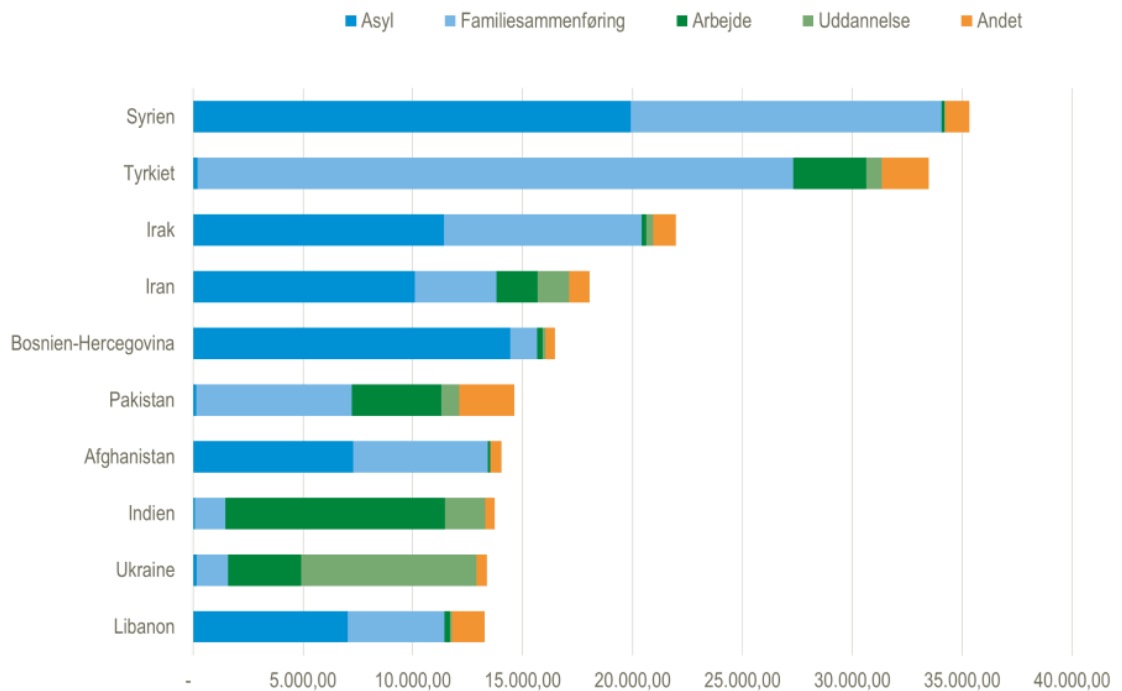
#### 1.3.1.1. Overall

Complications of diabetes are traditionally divided into macrovascular (e.g. *cardiovascular disease* (CVD)) and microvascular complications (e.g. kidney disease, retinopathy, neuropathy), all of which contribute to morbidity and mortality in T2D. Several lifestyle and physiological factors influence the risk of developing complications, and clinical care

## 1. Introduction



(a) Reason for migration: Western countries



(b) Reason for migration: Non-western countries

Figure 1.2.: Primary reason for migration among the 10 largest migrant groups in Denmark from Western (a) and Non-western countries (b). Adapted from Statistics Denmark.<sup>13</sup>

### 1.3. Type 2 diabetes care

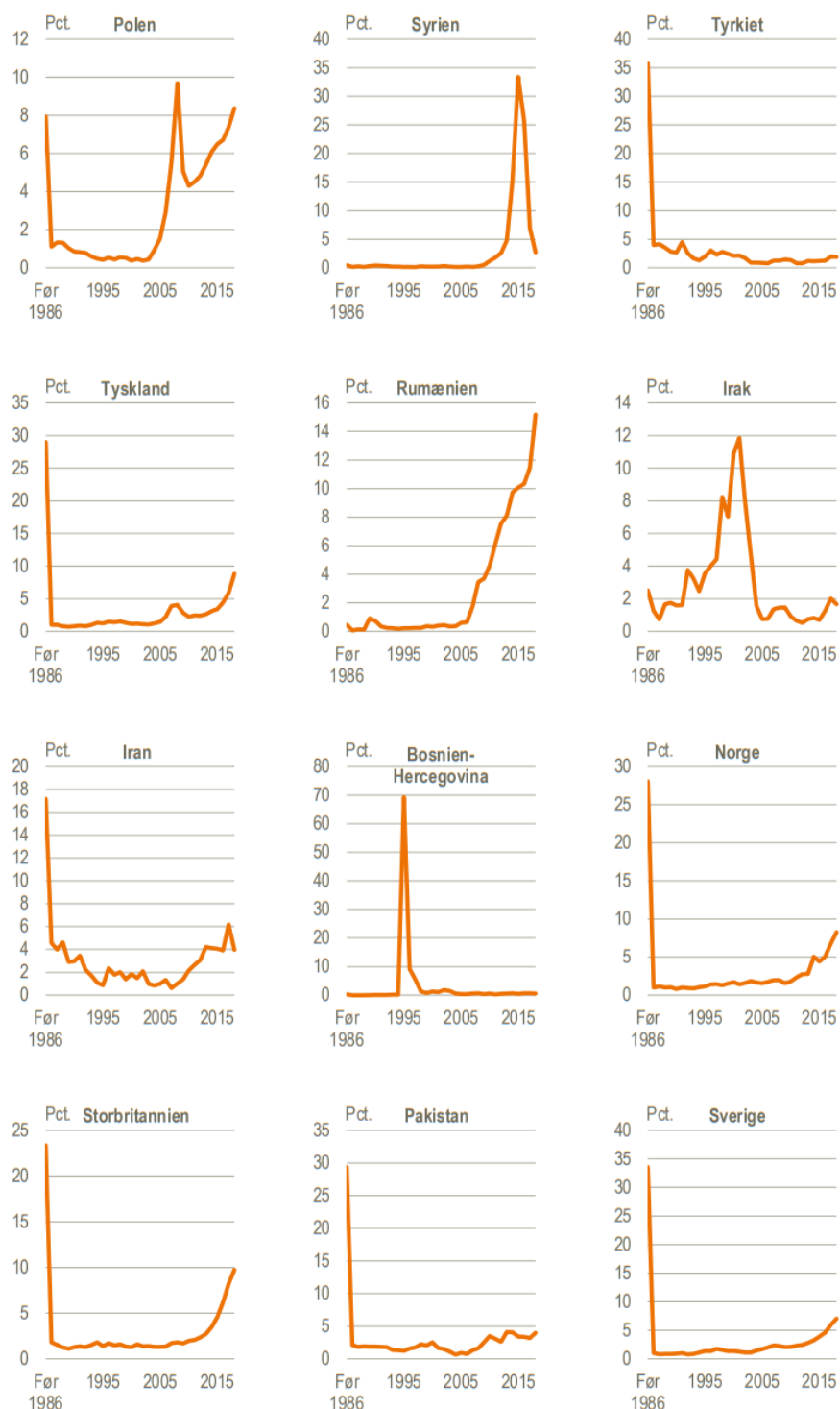


Figure 1.3.: Calendar year of first immigration among the 12 largest migrant groups residing in Denmark in 2019. Adapted from Statistics Denmark.<sup>12</sup>

revolves around management of these. In addition to being key risk factors of complications, blood pressure and levels of *hemoglobin-A1C* (HbA1c) and *low-density lipoprotein cholesterol* (LDL-C) drive indications for treatment and clinical decision-making in T2D[manglerref].

### 1.3.1.2. In migrants

In European countries, HbA1c-levels are higher in migrants than in native populations[manglerref], but LDL-C levels have only been sparsely described. The evidence on complication risk is inconsistent, but indicates a higher risk compared to native populations, although risks differ between complication types, migrant groups and countries. Similarly, higher mortality among migrants with T2D has been reported in some studies [refs], while other studies have found similar or lower risk [manglerrefs]

### 1.3.2. Pharmacological treatment

#### 1.3.2.1. Overall

Due to their effects on HbA1c, LDL-C, and blood pressure, *glucose-lowering drugs* (GLD), *lipid-lowering drugs* (LLD), and antihypertensive drugs are critical parts of T2D care. In T2D patients with particularly high risk of complications, pharmacological treatment also includes *antiplatelet therapy* (APT), as the complication risk-lowering effect outweighs the risk of adverse events in these patients<sup>18,19</sup>. In addition to their effect on biomarker levels, certain drug types within the above classes of drugs have other positive effects. In particular, the GLD types *sodium glucose co-transporter type 2 inhibitors* (SGLT2i) and *glucagon-like peptide-1 receptor agonists* (GLP1RA) substantially reduce the risk of adverse cardiovascular and renal events beyond their effect on HbA1c. Similarly, the antihypertensive drugs types *angiotensin-converting enzyme-inhibitors* (ACEI) and *angiotensin receptor blockers* (ARB) reduce the risk and improve the prognosis of *diabetic kidney disease* (DKD) beyond their effect on blood pressure. [manglerref]

Combination therapy - the use of multiple drug types with differing mechanisms of action - is a way to increase treatment intensity and achieve treatment goals with fewer side-effects. Combination therapy is particularly important in T2D, as GLD monotherapy fails to achieve target levels of HbA1c in many patients, even at maximal dosage. [manglerref]

### 1.3.2.2. In migrants

Evidence from several European countries shows that GLDs are prescribed earlier and/or to a larger proportion of migrants compared to native populations[manglerref]. However, disparities in the quality of the prescribed GLD treatment, such as the use of combination therapy or the types of GLD prescribed, has not been studied. Indirect evidence suggests that such disparities are likely, as non-white minorities in the UK were slower and less likely to intensify to combination therapy than white groups[manglerref9], and migrants in Italy with T2D purchased fewer packages of non-insulin GLD per person-year than their native counterparts[manglerref10], and socioeconomic[manglerref21-25] and racial[manglerref22, 24, 27] disparities in prescribing of SGLT2i and GLP1RA have been reported in several countries.

In contrast, studies from European countries have reported lower rates of prescribing of LLD in migrants with T2D [*care\_qual\_migrants refs 40, 5, Eastwood*]. Treatment with LLD is not indicated in all patients with T2D, however, and only a few of these studies accounted for treatment indication.

Evidence on ACEI/ARB use and APT in migrants with T2D is very limited, but a study from Italy found lower odds of treatment in most migrant groups [42], indicating a potential for disparities in these areas of care.

### 1.3.3. Monitoring

#### 1.3.3.1. Overall

In T2D, timely monitoring of risk factors and complications allows faster adjustment of treatment, and monitoring has previously been used as a process indicator of care quality, although the direct evidence on its influence on outcomes is sparse. [*see refs [7-12, e.g. <https://doi.org/10.1093/intqhc/mzl023>, , evt. DVDD rapport]*]\*

#### 1.3.3.2. In migrants

The evidence on monitoring of T2D in migrants is inconsistent between countries and different aspects of monitoring. In Norway, migrants with T2D received similar or more monitoring than native Norwegians[manglerrefTran2010], while migrants with T2D in Italy received fewer referrals for consultations than native Italians[manglerrefMarchesini2014].

### 1.4. Clinical guidelines for type 2 diabetes care

In Denmark, T2D care is most often provided by *general practitioners* (GPs) and other actors in the primary care sector, although some patients are treated in the outpatient hospital setting. The Danish College of General Practitioners publishes national clinical guidelines for T2D in cooperation with the Danish Endocrine Society. The guidelines are continuously updated as new evidence emerges. In this PhD project, T2D care was studied in the time period covered by the 2012<sup>20</sup> and 2019<sup>21</sup> revisions (only minor changes were made between the two revisions). These guidelines advise that monitoring intervals, biomarker goals and treatment intensity are adapted to fit the individual patient, but specify recommendations that may be used as indicators of care quality.

Danish guidelines provide virtually no specific recommendations on T2D care in migrants, and migrants are not addressed in the appendix on pharmacological treatment of special groups. Guideline recommendations relevant to this PhD study are described below.

#### 1.4.1. Diagnosis

HbA1c values  $\geq 48\text{mmol/mol}$  are diagnostic of type 2 diabetes, but diagnosis must be confirmed with a repeated sample on a different day. Once diagnosed, patients with T2D should be considered permanently affected by the disease, and the associated risk factors for complications should be treated regardless of subsequent normalization of HbA1c.

Migrant origin is mentioned as a risk factor of T2D, and guidelines recommend increased HbA1c screening in certain migrant groups.

#### 1.4.2. Monitoring

The risk biomarkers HbA1c and LDL-C should be measured yearly, as well as urine albumin-to-creatinine ratio (UACR) to screen for DKD. Repeated samples of UACR  $\geq 300\text{mg/g}$  is considering diagnostic of diabetic kidney disease (DKD). Diabetic retinopathy should be screened by an ophthalmologist every second year and screening for diabetic foot disease by a podiatrist every year. At the initial diagnosis of T2D, a baseline-screening of all five types of monitoring is recommended.

Guidelines provide no specific recommendations on monitoring in migrants.



### 1.4.3. Biomarker levels

For HbA1c, the goal should be the lowest possible level without hypoglycemia or inappropriate polypharmacy. Specific targets at  $48\text{mmol/mol}$ ,  $53\text{mmol/mol}$ ,  $58\text{mmol/mol}$ , and  $70\text{mmol/mol}$  are provided depending on diabetes duration and severity, complications, age and comorbidities.

For LDL-C, the level should be as low as possible. A general target below  $2.6\text{mmol/L}$  is provided, while the target in patients with complications should be below  $1.8\text{mmol/L}$ .

Guidelines provide no specific recommendations on HbA1c or LDL-C targets in migrants.

### 1.4.4. Pharmacological treatment

#### 1.4.4.1. Glucose-lowering drugs

**Combination therapy:** GLD therapy is recommended in patients with HbA1c  $\geq 48\text{mmol/mol}$ , and metformin is the recommended first-line treatment. There is no overall recommendation of second- or third-line drugs, although SGLT2i or GLP1RA should be considered in patients with CVD when metformin or other treatment is insufficient to reach the patient's HbA1c target (note that, although not in effect during the time period studied in this PhD project, the recommendations for SGLT2i and GLP1RA were expanded in the 2022 revision to include all T2D patients with CVD, multiple risk factors for CVD, or chronic kidney disease, irrespective of HbA1c level).

**Individual drug types:** Guidelines recommend factoring in all effects - positive and negative - as well as cost when choosing between individual drug types, and do not present a fixed hierarchy between GLD drug type. [*maybe summarise guideline considerations on second- and third-line drugs, similar to <https://vejledninger.dsam.dk/media/238.png>*]

#### 1.4.4.2. Lipid-lowering drugs

Treatment with LLD is recommended to all individuals with prevalent CVD, diabetic nephropathy, or LDL-C above  $2.5\text{mmol/L}$ .

### 1.4.4.3. Antihypertensive drugs

In addition to treatment of hypertension, use of either ACEI or ARB is recommended in individuals with prevalent CVD, microalbuminuria, or diabetic kidney disease.

### 1.4.4.4. Antiplatelet therapy

APT is recommended in individuals with prevalent CVD, diabetic kidney disease or very high risk of CVD due to other risk factors (this recommendation was expanded in the 2022 revision to also include individuals with kidney failure and concurrent microalbuminuria).

Guidelines provide no specific recommendations on any aspect of pharmacological treatment in migrants.

## 1.5. Identification of type 2 diabetes cases in healthcare registers

### 1.5.1. Danish register data infrastructure

What is collected on whom, and how?

How is the data structured and stored, who can get access - to what, and how?

Researchers get access to the same raw data, stored in the same structure (unless a data manager on the recipient end edits the raw data during the access data transfer process)

The shared data potentially enables reproducible research, if code were also shared publicly (which it is not).

### 1.5.2. Benefits

Healthcare registers provide a powerful data source for population-wide studies without the need to engage the patient for inclusion. The ability to include all individuals in the population makes them particularly suited for studies of migrants with T2D, where sample size is a limiting factor and other data sources may be vulnerable to selection bias in these groups.

### 1.5.3. Challenges

General-purpose registers and other administrative databases often provide the basis of diabetes epidemiology, but rarely contain validated diabetes-specific data. If the diabetes-specific data is not accurate, bias may be induced into studies. Thus, it is important to have an accurate tool to identify individuals with diabetes in the registers, as findings may differ with various diabetes definitions. Considerable efforts have been made towards establishing such a tool for diabetes research in several countries, including Denmark.

Internationally, some algorithms classifying T1D and T2D have been validated in cohorts of individuals with diabetes, but none have been validated in a general population. In a general population, classification algorithms (classifiers) must not only discern type 1 diabetes (T1D) from T2D, but also identify diabetes while accounting for events that might lead to inclusion of non-cases, such as use of GLD in the treatment of other conditions. Currently, no type-specific diabetes classifier has been validated in a general population, which leaves register-based studies in this area vulnerable to biases.

### 1.5.4. Register-based diabetes classifiers

In Denmark, the first resource readily available to researchers to identify diabetes cases using register data was the National Diabetes Register, established in 2006. The National Diabetes Register was discontinued in 2012, and a later validation study questioned its validity and called for future registers to adopt inclusion based on elevated HbA1c levels.

Currently, the Register of Selected Chronic Diseases (RSCD) is the only publicly available resource to identify diabetes cases in Danish register data (by application to the Danish Health Data Authority), but it has not been publicly validated nor is the source code behind the algorithm publicly available. Notably, the algorithm lacks inclusion based on elevated HbA1c levels.

## 1.6. Introduction at a glance

T2D is a disease that carries serious risks, but several treatment options are available to control the risk factors in T2D and reduce the risk of complications and death. In an aging population, the burden of T2D on healthcare services is rising, and resources must be prioritized to those with higher needs to ensure adequate care.

Migrants are particularly vulnerable to T2D, having an increased prevalence of the disease compared to native Danes. Despite having higher HbA1c levels than their native counterparts, evidence on complication risk and mortality in migrants is inconsistent, but some evidence suggests a higher risk. Evidence on disparities in care that may contribute excess risk in migrants with T2D is limited, and research in this area faces several challenges that may explain this, such as limited sample sizes and migrants being hard-to-reach for intervention and survey studies. Register-based studies are well-suited to handle these limitations, but currently there is no validated method to identify T2D cases in a general population, which leaves register-based studies in this area vulnerable to biases.

In Denmark, guidelines are available to direct clinicians and patients towards the best possible outcomes while prioritizing resources. Despite the special challenges facing migrants, current guidelines do not contain specific recommendations for T2D care in migrants, perhaps due to the limited evidence on specific areas of T2D care where disparities between migrant groups and native Danes may be present.

## 2. Aims

### 2.1. Overall aims

The overall aim of this PhD dissertation is to provide robust knowledge on specific areas of T2D care where disparities between migrant groups and native Danes may be present.

### 2.2. Specific aims

- I. Develop a register-based classification of type 1 and type 2 diabetes and make it available to other researchers.
- II. Validate register-based diabetes classifiers available to researchers in Denmark.
- III. Assess prevalence of T2D in migrant minorities of Denmark, and explore disparities between migrant groups and native Danes in indicators of guideline-recommendations on monitoring, biomarker control, and pharmacological treatment.
- IV. Evaluate disparities in the quality of glucose-lowering pharmacological treatment between migrants and native Danes in terms of combination therapy and drug types.

### 2.3. Outputs

Aims II, III, and IV were pursued in the respective papers I, II, and III associated with this dissertation, while aim I was pursued in the creation of the open-source R package *osdc*.

## 3. Material and methods

### 3.1. Setting

#### 3.1.1. The Danish healthcare system

*[Describe the danish public healthcare system: sectors, actors, reimbursement and patient-incurred costs.]*

Denmark is divided into 5 administrative regions that are responsible for providing public healthcare services to their residents through public hospitals and contract agreements with private actors in the primary care sector. Private actors include GPs and other specialist practices (e.g. ophthalmologists), as well as other healthcare professionals (e.g. podiatrists). In addition, the 98 Danish municipalities are obliged to offer resources to prevent and/or manage chronic disease, such as programs on managing T2D through diet and physical exercise.

Although referral to outpatient hospital care is possible, patients with T2D are primarily treated at the GP, which native Danes and migrants with residence permit have free access to. In the tax-funded Danish public healthcare system, Danish citizens and migrants with residence permit have equal access to services, and nearly all services are provided free of charge, although T2D patients incur some out-of-pocket co-payments for podiatrist care and prescription drug purchases at pharmacies. Yearly co-payments towards medication expenditures are partially covered from €132 and expenditures beyond €553 are fully covered (2019 limits),<sup>22</sup> while 50% of all expenditures towards diabetes-specific podiatrist care are covered by the the public health insurance.<sup>23</sup>

### 3.2. Data sources

*[Describe the overall CPR number system and acquisition and how it related to civil registration, healthcare contacts and prescription drug use, and how it allows linkage of the data sources.]*

The Danish registers contain

Data for this study was gathered from several sources and linked on an individual level using the unique personal identifier given to all Danish residents at immigration or birth. Civil registration, all healthcare contacts and drug prescriptions in Denmark are recorded with this identifier, thus enabling complete data linkage and coverage of the entire population.

### 3.2.1. The Danish Civil Registration System

CRS ref

### 3.2.2. The Danish National Patient Register

NPR ref Validation refs e.g. for CVD goes in discussion chapter 5.

### 3.2.3. The Danish National Health Service Register

NHSR ref

### 3.2.4. The Danish National Prescription Registry

NPrR ref

### 3.2.5. The Danish Register of Laboratory Results for Research

RLRR ref? RLRR covers all of Denmark...

### 3.2.6. The Clinical Laboratory Information System of Central Denmark Region

At the time of data acquisition, RLRR did not yet cover the Central Denmark Region, and laboratory results from this part of the the population was extracted from the CLIS/LABKA ref

## 3.3. Diabetes classification algorithms

*[A short intro on why we decided to develop a novel algorithm to classify diabetes instead of just validating the existing classifier].* Introduce OSDC and RSCD abbreviations

As a point of reference in validation, we developed an implementation of the algorithms of the RSCD diabetes classifier (version 1.0, August 2016) according to official documentation.<sup>27</sup>

The following sections describe the algorithms behind each diabetes classifier.

*[detailed discussion of choices in OSDC, e.g. on obstetric coding, and pros/cons of RSCD goes in chapter 5]*

### 3.3.1. The Open-Source Diabetes Classifier

*[CP from validation paper]*

### 3.3.2. The Register of Selected Chronic Diseases

*[CP from validation paper]*

## 3.4. Validation Questionnaire data

### 3.4.1. The Health In Central Denmark survey

Describe population, inclusion, responses etc. HICD ref

### 3.4.2. The National Health Survey

Describe population, inclusion, responses etc. NHS ref. This survey was only used for supplementary validation analyses.



### 3.5. Study design and population

Study I was designed to examine the validity of register-based definitions of T1D and T2D, the latter of which was used to identify the population-wide study populations in studies II and III.

*[Overview table of the three studies]*

#### 3.5.1. Study populations

##### 3.5.1.1. Study I

From nationwide healthcare registers, data covering the Central Denmark Region was used to identify diabetes populations using the OSDC and RSCD classifiers.

##### 3.5.1.2. Study II

*[Describe the different study populations in the analyses of study II, “indication for treatment”, and the reason for exclusions]*

##### 3.5.1.3. Study III

*[Describe the study populations in study III]*

#### 3.5.2. Outcomes

##### 3.5.2.1. Study I

The validation outcomes

##### 3.5.2.2. Study II

Prevalence and the indicators of care quality

##### 3.5.2.3. Study III

*Combinations therapy and individual drug types*

#### 3.5.2.4. Timeline of all outcomes across the three studies

Make a figure.

#### 3.5.3. Primary variable of interest: migrant status

*[CP from papers]*

#### 3.5.4. Other explanatory variables

*[CP from papers]*

### 3.6. Statistical analysis

#### 3.6.0.1. Study I

Validation: Introduce sensitivity, PPV and other validation metrics.

#### 3.6.0.2. Study II & III

Robust poisson regression. Why we chose the models that we did.

### 3.7. Ethics and approval

## 4. Results in summary

*[Align structure with each individual study? Or split into themes? Kind of doing both for now]*

### 4.1. Study I

In this study, we identified... Number of participants, diabetes cases etc.

#### 4.1.1. Register-based classification of type 1 diabetes

metrics

#### 4.1.2. Register-based classification of type 2 diabetes

metrics

### 4.2. Study II

[Maybe for each outcome?] In this study, we identified... Number of participants, diabetes cases etc.

### 4.2.1. Prevalence

### 4.2.2. Monitoring

### 4.2.3. Biomarker control

### 4.2.4. Pharmacological treatment

### 4.2.5.

## 4.3. Study III

In this study, we identified... Number of participants, diabetes cases etc.

### 4.3.1. Combination therapy

### 4.3.2. Drug types

## **5. Discussion of methods**

### **5.1. Study designs**

### **5.2. Internal validity**

#### **5.2.1. Selection bias**

#### **5.2.2. Information bias**

T2D was validated! Diabetes duration Migrant ethnicity based on country of origin is more accurate than race or continent, but does not capture ethnic differences within the countries of origin.

#### **5.2.3. Confounding**

Studies II and III mapped risks, not causal associations

### **5.3. External validity**

#### **5.3.1. Generalizability**

Population-wide: representative of the Danish healthcare system and migrant populations in their current state. Risks are likely to be representative of other, similar healthcare systems and migrant populations found in other Nordic countries - but not in other contexts.

Migrant group characteristics, such as distribution of other covariables may provide different results between countries, as well as difference outcome prevalence in the native population.

### 5.4. Analyses

Robust poisson regression provides more intuitive estimates of relative risk than logistic regression in studies where the outcome of interest is not rare.

## 6. Discussion of results

### 6.1. Key main findings

Register-based classifiers identified valid populations of T1D and T2D in a general population, but diabetes type in cases with atypical age at onset of diabetes should be interpreted with caution.

Disparities between migrant groups and native Danes, yes, but much can be attributed to differences in clinical characteristics. Largest disparities in podiatrist monitoring, control of HbA1c and LDL-cholesterol and GLP1RA use. Migrants from Somalia received “poorer” care in all outcomes, and poorest care of all groups in most.

In the following sections, the main findings out each study will be discussed separately in light of existing literature.

#### 6.1.1. Study I

*[probably mostly CP from paper?]*

#### 6.1.2. Study II

*[probably mostly CP from paper?]*

#### 6.1.3. Study III

*[probably mostly CP from paper?]*

## 7. Conclusions and implications

### 7.1. Main conclusions

*[probably mostly CP from papers]*

### 7.2. Implications

Validation: Diabetes researchers can trust OSDC and RSCD, and very likely also classifiers with similar algorithms used on similar source data and populations.

osdc-package

Atypical age at onset of diabetes

Migrants:

*[Structure similar to discussion in paper III]*



## 8. Perspectives and future research

### 8.1. Perspectives

The findings call for bla bla bla updated guidelines, increased awareness....

Action card for physicians: which areas of care to pay particular attention in each migrant group, when delivering care to a migrant with T2D.

### 8.2. Future research

Validated diabetes classifiers, or similar, should be used. Validation studies on diabetes duration/age at onset of diabetes should be performed.

Qualitative studies? The reasons for the observed disparities should be studied, and intervention studies are needed to address these reasons in migrants in an evidence-based way.

Other vulnerable groups?

## References

1. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice* [Internet] 2022;183:109119. Available from: <https://www.sciencedirect.com/science/article/pii/S0168822721004782>
2. Danmarks Statistik [Statistics Denmark]. Befolkningsfremskrivning: Indvandrere og efterkommere [English: Population projection: Immigrants and descendants] [Internet]. {2019-2039; last accessed on 7 Feb 2023}; Available from: <https://extranet.dst.dk/pyramide/pyramide.htm#!y=2039&o=2019&c=4>
3. Erayil SE, Smith MK, Gebreslasse T, et al. The value and interpretation of race and ethnicity data in the era of global migration: A change is in order. *The American Journal of Tropical Medicine and Hygiene* [Internet] 2021;105(6):1453–5. Available from: <https://www.ajtmh.org/view/journals/tpmd/105/6/article-p1453.xml>
4. UNHCR. “Refugees” and “Migrants” – Frequently Asked Questions (FAQs) [Internet]. {2016; last accessed on 7 Feb 2023}; Available from: <https://www.unhcr.org/en-us/news/latest/2016/3/56e95c676/refugees-migrants-frequently-asked-questions-faqs.html>
5. European Commission, Migration and Home Affairs. Country responsible for asylum application (Dublin Regulation) [Internet]. {last accessed on 7 Feb 2023}; Available from: [https://home-affairs.ec.europa.eu/policies/migration-and-asylum/common-european-asylum-system/country-responsible-asylum-application-dublin-regulation\\_en](https://home-affairs.ec.europa.eu/policies/migration-and-asylum/common-european-asylum-system/country-responsible-asylum-application-dublin-regulation_en)
6. The Danish Immigration Service. New to Denmark: You want to apply as a family member [Internet]. {last accessed on 7 Feb 2023}; Available from: <https://nyidanmark.dk/uk-UA/You-want-to-apply/Family>
7. The Danish Immigration Service. New to Denmark: You want to apply for a work permit [Internet]. {last accessed on 7 Feb 2023}; Available from: <https://nyidanmark.dk/uk-UA/You-want-to-apply/Work>
8. The Danish Immigration Service. New to Denmark: You want to apply for a residence and work permit as a student [Internet]. {last accessed on 7 Feb 2023}; Available from: <https://nyidanmark.dk/uk-UA/You-want-to-apply/Study>

9. The Danish Immigration Service. New to Denmark: Nordic citizens [Internet]. {last accessed on 7 Feb 2023}; Available from: <https://nyidanmark.dk/uk-UA/You-want-to-apply/Residence-as-a-Nordic-citizen-or-EU-or-EEA-citizen/Nordic-citizens>
10. Indenrigs- og Boligministeriet [English: Ministry of the Interior and Housing]. Vejledning om folkeregistrering, bilag 1: Registrering af hændelser i udlandet [English: Civil registration guidelines, appendix 1: Registration of events abroad] [Internet]. {2013; last accessed on 7 Feb 2023}; Available from: <https://www.retsinformation.dk/eli/retsinfo/2013/9273#Bill>
11. Danmarks Statistik [English: Statistics Denmark]. Indvandrerne medbragte uddannelse [English: Education carried by immigrants] [Internet]. {2020; last accessed on 7 Feb 2023}; Available from: <https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=formid&fo=medbragt-udd--pdf>
12. Danmarks Statistik [English: Statistics Denmark]. Indvandrere i Danmark 2019 [English: Immigrants in Denmark 2019] [Internet]. {2019; last accessed on 7 Feb 2023}; Available from: <https://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=29446&sid=indv2019>
13. Danmarks Statistik [English: Statistics Denmark]. Fakta om indvandrere og efterkommere i Danmark [English: Facts on immigrants and descendants in Denmark] [Internet]. {2022; last accessed on 7 Feb 2023}; Available from: <https://www.dst.dk/da/Statistik/nyheder-analyser-publ/bagtal/2022/2022-08-18-fakta-om-indvandrere>
14. Kaneshiro B, Geling O, Gellert K, Millar L. The challenges of collecting data on race and ethnicity in a diverse, multiethnic state. *Hawaii Med J* 2011;70(8):168–71.
15. United Nations Statistics Division. Standard country or area codes for statistical use (M49) [Internet]. {2022; last accessed on 7 Feb 2023}; Available from: <https://unstats.un.org/unsd/methodology/m49/>
16. Statistics Denmark. Documentation of statistics for Population Projections 2019 [Internet]. {2019; last accessed on 7 Feb 2023}; Available from: <https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=49459100303&fo=0&ext=kvaldel>
17. Bennet L, Udumyan R, Östgren CJ, Rolandsson O, Jansson SPO, Wändell P. Mortality in first- and second-generation immigrants to Sweden diagnosed with type 2 diabetes: A 10 year nationwide cohort study. *Diabetologia* 2021;64(1):95–108.
18. Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *New England Journal of Medicine* [Internet] 2011;364(10):907–17. Available from: <https://doi.org/10.1056/NEJMoa1007994>

19. Zoungas S, Galan BE de, Ninomiya T, et al. Combined Effects of Routine Blood Pressure Lowering and Intensive Glucose Control on Macrovascular and Microvascular Outcomes in Patients With Type 2 Diabetes: New results from the ADVANCE trial. *Diabetes Care* [Internet] 2009;32(11):2068–74. Available from: <https://doi.org/10.2337/dc09-0959>
20. The Danish College of General Practitioners [Dansk Selskab for Almen Medicin]. Type 2-diabetes - et metabolisk syndrom [English: Type 2 diabetes - a metabolic syndrome] [Internet]. {2012; last accessed on 7 Feb 2023}; Available from: <https://vejledninger.dsam.dk/media/files/20/type-2-diabetes-2012-med-links.pdf>
21. The Danish College of General Practitioners [Dansk Selskab for Almen Medicin]. Type 2-diabetes - opfølgning og behandling [English: Type 2 diabetes - follow-up and treatment] [Internet]. {2019; last accessed on 7 Feb 2023}; Available from: <https://vejledninger.dsam.dk/type2/>
22. Danish Medicines Agency. Reimbursement thresholds [Internet]. {2023; last accessed on 7 Feb 2023}; Available from: <https://laegemiddelstyrelsen.dk/en/reimbursement/calculate-reimbursement/reimbursement-thresholds/>
23. Danish Regions. OKPortal: Takstmapper [English: Contract agreement Portal: Rate folders] [Internet]. {2023; last accessed on 7 Feb 2023}; Available from: <https://okportal.dk/Default.aspx?area=Praksis&type=Takstmapper>

## English summary

This is what I spent three years on...

## Dansk resumé

Det her brugte jeg tre år på...

# A. Supplementary material

Some results that wouldn't fit into the main thesis

## A.1. To do/Questions:

- Translate figures from DST

### A.1.1. Introduction:

#### A.1.1.1. Clinical guidelines:

Historisk udvikling/perspektiv

Hvordan i udlandet? UK: intet. Sverige: intet. Norge: lidt-til-intet. Holland: Helius?

HbA1c øget? screening

Noget om hæmoglobinopatier og gdm.

Individuelle mål for monitorering osv.

#### A.1.1.2. Register-data

Værdien

Hvem/Hvordan fås adgang og hvad får man adgang til.

### A.1.1.3. Old

## A.2. Various snippets

While migrant origin in research is often a simple variable used to capture socioeconomic position, it reflects both genetic disposition, cultural ethnicity, and potential language barriers, mental and physical trauma. *[mangler ref]*

Historically, particularly in Europe and the United States, migrants have been defined by their racial appearance, and ethnic minority groups categorized accordingly. In research, these categories obscure the role of migrants in the modern era,<sup>3</sup>. *[something about how the sparse evidence on T2D in ethnic minorities is often based on race, which doesn't capture ethnicity in the modern era of global migration very well, and very little direct evidence is available on T2D in migrants]*.