The various colours of type 2 diabetes: Pathogenesis and epidemiology in different ethnic groups
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General Introduction
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“Someone in the world dies of causes related to diabetes every eight seconds... in the same seconds, another two people contract the illness.”
- Michael Hirst, President International Diabetes Federation -

A wealth of epidemiological data has shown that the prevalence of type 2 diabetes mellitus has increased over recent years and continues to increase at an alarming rate across the entire world. According to the International Diabetes Federation, the reported worldwide prevalence of diabetes mellitus in 2012 was 371 million (8.3 %), with projections that by 2030, the prevalence will have reached 552 million (9.9%) (1). Unfortunately, the actual number of people with diabetes is estimated to be even higher, as population-based diabetes studies have consistently shown that up to 50% of those with diabetes remain undiagnosed, largely because there are few symptoms during the early years of type 2 diabetes and symptoms may not be recognised as being related to diabetes (2). The vast majority of those with diabetes mellitus have type 2 diabetes, which makes up about 85 to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle-income countries. Type 2 diabetes is therefore considered a global health threat, which, in most countries, has developed in synchrony with rapid cultural and social changes, such as ageing populations, increasing urbanisation, dietary changes, reduced physical activity, and increase of other unhealthy behaviours.

Several studies have focused on comparing the frequency of diabetes in the same ethnic group in different environments, and in different ethnic groups sharing the same environment. These experiences have shown us that certain ethnic groups are disproportionately affected by diabetes mellitus and its complications (3-7). This is especially true for people of South Asian and African origin; when compared to those from European origin, the diabetes prevalence is much higher in these individuals. Furthermore, while type 2 diabetes in people from European origin usually becomes apparent over the age of 40, it often manifests itself before the age of 40 among South Asians and African origin populations (4,5,7,8). In addition, higher mortality rates and a higher risk of diabetes complications have been reported in these groups (8,9). The exact reasons for these ethnic disparities are multifactorial and complex.

The main aim of this thesis was to investigate ethnic differences in the pathogenesis of type 2 diabetes and to determine the effectiveness of several preventive and therapeutic strategies in ethnic groups that are known to be disproportionately affected by diabetes.
Before explaining the outline of the thesis, the definition of the term ‘ethnicity’ needs to be addressed. Until the second half of the twentieth century, race - as defined by physical appearance characteristics such as skin colour, eye shape, and facial structure - was considered a useful way of classifying people into ethnic groups. However, as there are no validated biological criteria on a phenotype level to determine an individual’s race, the term ethnicity has overtaken race in medical sciences (10). According to current definitions, an ethnic group can be defined as a group that has a shared history, ancestry, and identity, and that shares characteristics such as a geographical affiliation, culture and traditions, language, and religious tradition. For this reason, it is important to realize that an ‘ethnic’ difference in the prevalence of a disease may be the result of differences in various biological, behavioural and psychosocial factors. In medical research, frequently used indicators for ethnicity include country of birth, self-identified ethnicity, and nationality. In the vast majority of the studies included in this thesis, ethnicity is assessed according to self-identified ethnicity, together with the country of birth of the participants and their parents.

This thesis is structured in three parts. First, we focus on the identification of diabetes and prediabetes by means of different diagnostic criteria in people from South Asian origin. Second, we address differences in risk factors for type 2 diabetes and in the susceptibility to these risk factors between those from South Asian, African and European origin. Third, we investigate the effectiveness of certain preventive and therapeutic strategies in these ethnic groups. In each part of this thesis, several research questions will be addressed.

PART I: Identification of diabetes and prediabetes by means of different diagnostic criteria in people from South Asian origin

As mentioned, populations of South Asian origin are known to have a high risk of type 2 diabetes and cardiovascular diseases (3). For this reason, they form an important target group for active screening and prevention in clinical practice. However, diabetes nowadays can be identified in several ways, namely based on values of fasting plasma glucose, glycosylated haemoglobin A1c (HbA1c) or by means of an oral glucose tolerance test. The criteria chosen to identify type 2 diabetes or prediabetes may have quite an impact, as an incomplete overlap between OGTT- and HbA1c-based diagnoses of prediabetes and type 2 diabetes has been reported in populations of diverse ethnic origins (11-13). These discordances may occur because of measurement variability or because the HbA1c level and the OGTT hallmark different pathophysiological processes (14). This implies that the metabolic profiles, and therefore future risk, of these discordantly diagnosed individuals may differ. For this reason, we addressed the following research questions in Chapter 2:

1. What is the overlap between OGTT and HbA1c-based classifications of diabetes and prediabetes in people of South Asian origin?
2. Do South Asians who are diagnosed with prediabetes and diabetes by means of HbA1c levels have different metabolic profiles than those who are considered normal by HbA1c criteria but who would have been diagnosed with (pre)diabetes by an OGTT?

PART II: Risk factors for type 2 diabetes and the susceptibility to these risk factors

Although the criteria to identify type 2 diabetes yield discordant diagnosed individuals in various ethnic groups, true ethnic differences in the prevalence and incidence of type 2 diabetes exist, regardless of the method used. As mentioned, the explanation for these differences is complex. Common risk factors for type 2 diabetes in all ethnic groups include obesity, physical inactivity, prediabetes, genetic factors and simply being of an older age (15-17). However, the distribution of some of these risk factors for type 2 diabetes are known to differ between ethnic groups. For example, certain genetic polymorphisms predisposing individuals to insulin resistance seem to cluster in people from South Asian and African origin compared to those from European origin (18). Furthermore, ethnic differences in lifestyle factors such as diet and physical activity may contribute to differences in the diabetes incidence as well (8,19).

Apart from ethnic differences in the prevalence of risk factors for type 2 diabetes itself, the susceptibility to these risk factors may differ between ethnic groups. For example, at a similar age and body mass index (BMI) level, people from South-Asian origin develop type 2 diabetes more often than their counterparts from European origin (3). However, little is known on whether ethnic differences exist in the susceptibility to other risk factors, such as prediabetes and physical inactivity. Therefore, we focused on the following research questions in Chapter 3 and Chapter 4:

3. Do the associations of impaired fasting glucose and fasting plasma glucose with the 10-year cumulative incidence of type 2 diabetes differ between people of South Asian, African and European origin (Chapter 3)?

4. Does the association between physical inactivity and type 2 diabetes differ between people of South Asian, African and European origin (Chapter 4)?

It is important to realize that the extraordinary high risk of developing type 2 diabetes in certain ethnic groups, such as South Asians, may not be fully attributable to ethnic differences in the prevalence of traditional risk factors for diabetes or the susceptibility to these risk factors (5,8). It is likely that other, still unidentified causes contribute to the metabolically unfavourable position of these ethnic groups. One of these unidentified causes could be a relatively low brown adipose tissue activity. Given its high capacity to dissipate excess energy, brown adipose tissue has recently been identified as a possible target to fight
obesity and thus protect against type 2 diabetes (20-23). Brown adipose tissue can be assessed with various nuclear imaging techniques, of which $^{18}$F-fluoro-deoxyglucose ($^{18}$F-FDG) positron-emission-tomography (PET) computed-tomography (CT) is most commonly used, typically under conditions of mild cold exposure (20-22). Although knowledge of the exact mechanisms regulating brown adipose tissue activity in humans is still limited, it is likely that stimulation by the sympathetic nervous system is an important determinant of brown adipose tissue activity (21). It is well known that sympathetic stimulation of organs in humans can be visualized with the tracer $^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG, a radiolabeled norepinephrine analogue) (24,25). However, the sympathetic stimulation of brown adipose tissue has not been prospectively studied in humans. For this reason, we first aimed to establish $^{123}$I-MIBG single photon emission computed tomography (SPECT-CT) as a method to prospectively visualize and quantify the sympathetic stimulation of brown adipose tissue in humans (Chapter 5). Specifically, we formulated the following research questions:

5. Do $^{123}$I-MIBG SPECT-CT, as a measure of sympathetic stimulation, and $^{18}$F-FDG PET-CT, as a marker of metabolic activity, identify the same anatomical location of brown adipose tissue in adult lean humans? And how do the magnitudes of brown adipose tissue activity measured by these two techniques correlate?

Subsequently, we explored whether brown adipose tissue activity was lower in South Asians than in those from European origin. If so, this may contribute to the high risk of metabolic disturbances in South Asians. This resulted in the following research question (Chapter 6):

6. Are there differences in metabolic brown adipose tissue activity or in the sympathetic stimulation of brown adipose tissue between people of South Asian and European origin?

PART III: The effectiveness of preventive and therapeutic strategies
Knowledge about ethnic disparities in risk factors for and pathogenesis of type 2 diabetes can help to develop adequate strategies for both the prevention of and treatment of type 2 diabetes. The opportunity to reduce obesity and to prevent type 2 diabetes among high-risk individuals through intensive lifestyle intervention has been established in several efficacy trials (26-29). However, studies that have attempted to translate and implement the knowledge and expertise from these efficacy trials to clinical practice have achieved more moderate results (30-33). Despite these moderate effects, the authors of these studies conclude that lifestyle intervention may still be effective for reducing the risk of type 2 diabetes in high-risk groups (32,33). Indeed, it has been demonstrated that even a little weight loss may be accompanied by multiple beneficial changes in cardiovascular risk factors in high-risk groups (32). Despite being disproportionally affected by the burden of type 2 diabetes, the
effectiveness of intensive lifestyle interventions among high-risk South Asian populations in industrialized countries has not been determined. Therefore, the following question was addressed in Chapter 7:

7. What is the effectiveness after 1 year of a culturally targeted, intensive lifestyle intervention, on the weight status and metabolic profile of South Asians at risk of type 2 diabetes registered in general practices in the Netherlands?

When prevention fails, there is a spectrum of interventions to be considered for the treatment of type 2 diabetes. One of the most drastic options is bariatric surgery. Bariatric surgery is considered highly effective in morbidly obese patients. In fact, bariatric surgery has not only shown to induce weight loss, but also to ameliorate or eliminate type 2 diabetes, hypertension, and lipid abnormalities. (34-36). Having said that, the beneficial results following bariatric surgery appear to differ inter-individually; indeed, it is postulated that the effectiveness of bariatric surgery, in terms of weight loss, may vary between ethnic groups (37-39). Unfortunately, the data published concerning this topic are inconclusive, as most studies included only few patients from minority groups and/or did not find statistically significant differences between the ethnic groups studied. Furthermore, the vast majority of these studies have focused on African-Americans in comparison to white Americans (37-39). As a result, little is known about differences in outcomes after bariatric surgery between patients from other ethnic backgrounds. For these reasons, we addressed the following questions in Chapter 8 and Chapter 9:

8. Are suggestions of a difference in weight loss and diabetes remission after bariatric surgery between patients from African and European origin upheld in a systematic review and meta-analysis (Chapter 8)?

9. Are there differences in the effectiveness of bariatric surgery in patients of ethnic Dutch origin and their African, South-Asian, Turkish and Moroccan counterparts (Chapter 9)?

An overview of the studies covered in this thesis is given in Table 1 of this chapter. Furthermore, in Chapter 10, the most important findings of this thesis will be summarised and clinical implications of the findings, as well as advices on future directions, will be discussed.
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<th>Title</th>
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<td>Prevalence type 2 diabetes Prevalence prediabetes Specificity/sensitivity HbA1c Metabolic profile</td>
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<td>3</td>
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</tbody>
</table>

HbA1c, haemoglobin A1c; OGTT, oral glucose tolerance test; IFG, impaired fasting glucose; $^{123}$I-MBG, $^{123}$I-metaiodobenzylguanidine; CT, computed tomography; SPECT, single photon emission CT; $^{18}$F-FDG, $^{18}$F-fluoro-deoxyglucose; PET, positron emission tomography
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