The various colours of type 2 diabetes: Pathogenesis and epidemiology in different ethnic groups
Admiraal, W.M.

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Summary
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%).

Several studies have reported that certain ethnic groups are disproportionally affected by diabetes mellitus and its complications. 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. In addition, higher mortality rates and a higher risk of diabetes complications have been reported in these groups. 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 disproportionally affected by diabetes.

In Chapter 1, we described the background and outline of this thesis.

In Chapter 2, we evaluated the overlap between OGTT and HbA1c-based classifications of diabetes and prediabetes in people of South Asian origin. Furthermore, we compared the metabolic profiles of individuals who were identified by HbA1c with the metabolic profiles of those who were missed by the HbA1c measurement but which the OGTT could have identified. We found that we identified fewer new cases of diabetes, but more new cases of prediabetes with the HbA1c method than we did with the OGTT. Moreover, the overlap of the classifications based on the HbA1c level and the OGTT was only partial. Regardless of the partial overlap, we found that all those identified had poor metabolic profiles: for both diabetes and prediabetes, the metabolic profiles of those identified with HbA1c and those identified with the OGTT alone did not differ.

In Chapter 3, we determined whether the associations of impaired fasting glucose (IFG) and fasting plasma glucose (FPG) with the 10-year cumulative incidence of type 2 diabetes differed between people of South Asian, African and European origin. We found a much higher 10-year cumulative incidence of type 2 diabetes among those from South Asian and African origin than among those from European origin. This ethnic difference was even more striking for those with IFG than for those with normoglycemia at baseline. In line with this finding, we observed that the associations of both baseline IFG and FPG with incident type 2 diabe-
tes were stronger among those of South-Asian and, to a lesser extent, African origin than among those of European origin. This difference in associations between the ethnic groups persisted after adjustment for other well-known risk factors for type 2 diabetes. Our findings do not only confirm the high risk of type 2 diabetes in South Asians, but also suggest a more rapid conversion from IFG to type 2 diabetes in those of South Asian and African origin than in those of European origin.

In **Chapter 4**, we investigated the association between physical inactivity and type 2 diabetes in people of South Asian, African and European origin. We found that physical inactivity was associated with type 2 diabetes after adjustment for multiple risk factors in the total population. However, this association was only significant and appeared stronger in those from European origin than in those from African and South Asian origin. These results underscore the importance of exercise, but also suggest that the potential health gain may differ between ethnic groups.

In **Chapter 5**, we established $^{123}$I-MIBG single photon emission computed tomography ($^{123}$I-MIBG SPECT-CT) as a method to prospectively visualize and quantify the sympathetic stimulation of brown adipose tissue (BAT) in humans. We found that $^{123}$I-MIBG SPECT-CT, as a marker of sympathetic activity and $^{18}$F-FDG PET-CT, as a marker of metabolic activity, identified the same anatomical regions as active BAT. Moreover, when the $^{123}$I-MIBG SPECT-CT was performed 24 hours after $^{123}$I-MIBG administration, the magnitude of BAT activity measured with these techniques correlated strongly. This not only supports that BAT activity in humans is sympathetically influenced, but also identifies $^{123}$I-MIBG SPECT-CT, when performed 24 hours after $^{123}$I-MIBG injection, as a method to visualize and quantify sympathetic stimulation of BAT.

In **Chapter 6**, we explored whether BAT 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. We found no difference in BAT activity during cold exposure between those of European and South Asian origin. Furthermore, we observed no ethnic differences in factors influencing BAT activity. Although based on a small sample size, our data suggest that it is unlikely that brown adipose tissue plays an important role in the development of the unfavourable metabolic profile in populations of South-Asian origin.

In **Chapter 7**, we investigated the effectiveness after 1 year of an intensive, culturally targeted 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. We found that the lifestyle intervention did not result in improvement of weight status and metabolic profile.
in the target population. Our results show that realising a health benefit by means of an intensive lifestyle intervention among a high risk South Asian population in general practice is extremely difficult and that additional preventive strategies may have to be considered in order to achieve the intended health gain.

In **Chapter 8**, we determined whether differences exist in weight loss and remission of diabetes 1 year after bariatric surgery between people from African and European origin by means of a systematic review and meta-analysis. We found that patients from European origin lost more weight than patients from African origin, regardless of the type of bariatric surgery. Furthermore, while based on limited data, our meta-analysis suggested that despite the difference in weight loss, there are no statistically significant differences in remission of DM between these ethnic groups after surgery. In **Chapter 9**, we investigated whether there were similar differences in outcomes after bariatric surgery between individuals from other ethnic backgrounds. We found that in terms of weight loss, bariatric surgery was less effective in patients from African, South-Asian, Turkish and Moroccan origin than in ethnic Dutch subjects. Thus, ethnic differences in effectiveness of bariatric surgery are not limited to those between patients of European and African origin, but extend to other ethnic groups as well.

In **Chapter 10**, we discuss the main findings of this thesis and their implications for practice and further research. We concluded that ethnic background plays a role in the pathogenesis, prevention and treatment of type 2 diabetes. Therefore, when it comes to assessing a patients’ risk of type 2 diabetes, or developing preventive or therapeutic strategies for type 2 diabetes, it may be necessary to target strategies to specific ethnic groups. This thesis demonstrated that the risk of type 2 diabetes is much higher in people of South Asian and, to a lesser extent, African origin than in those from European origin. These ethnic differences in diabetes risk are even more striking in those with prediabetes. A possible explanation for these disparities might be an ethnic difference in the pathogenesis of type 2 diabetes. For example, the conversion from impaired fasting glucose to diabetes may be more rapid in South Asian and African individuals than in those from European origin, possibly as a result of faster progression of beta-cell failure in these groups.

The extraordinarily high incidence of diabetes, particularly in South Asians, warrants aggressive preventive approaches. Unfortunately, we found that a culturally targeted, intensive lifestyle intervention in clinical practice did not effectively change the weight and metabolic profile in South Asians with prediabetes. This does not imply that we should stop all health promotion activities in South Asians who already have prediabetes. In fact, we demonstrated that also in this population, weight loss can improve lipid profile and glucose metabolism. However, the extraordinarily high risk of type 2 diabetes in South Asians with
prediabetes, in combination with the disappointing lifestyle intervention results, suggest that merely fighting already existing metabolic disturbances is not enough. If we really want to curb the excessive burden of diabetes in those of South Asian origin, additional emphasis should lie on avoiding the development of these metabolic disturbances in the first place. In order to achieve this, education about a healthy lifestyle to prevent development of obesity and diabetes should be started as early as possible during childhood.