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

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General Discussion

In this chapter the findings of the studies included in this thesis will be discussed. First, a summary of the main findings will be given. Second, some general methodological issues will be addressed. Finally, the implications of the findings and advices for future research will be discussed.

Summary of the main findings
This thesis consisted of three parts. First, we focused on the identification of diabetes and prediabetes by means of different diagnostic criteria in people from South Asian origin. Second, we addressed differences in risk factors for type 2 diabetes and the susceptibility to these risk factors between those from South Asian, African and European origin. Third, we investigated the effectiveness of certain preventive and therapeutic strategies in these ethnic groups. This summary of the main findings is structured by the research questions, which were formulated in the general introduction, for each part of the thesis.

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

1. **What is the overlap between OGTT and HbA1c-based classifications of diabetes and prediabetes in people of South Asian origin?**

In Chapter 2, 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. Overall, the overlap of these methods for diabetes and prediabetes was partial: 51.6% of the participants with diabetes based on HbA1c levels also fulfilled the OGTT-criteria for diabetes. For prediabetes, this was 54.2%.

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?**

Regardless of the partial overlap between the diagnostic criteria, we found that participants who were diagnosed all had poor metabolic profiles. Those diagnosed based on their HbA1c levels did not have different metabolic profiles than those who were not identified based on HbA1c, but who could have been identified by an OGTT. This was the case for both diabetes and prediabetes.
PART II: Risk factors for type 2 diabetes and the susceptibility to these risk factors

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?

In Chapter 3, we found a 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 diabetes 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.

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

Physical inactivity was associated with type 2 diabetes after adjustment for multiple risk factors in the total study population (Chapter 4). However, when looking at the specific ethnic groups, this association was only statistically significant and appeared stronger in those from European origin than in those from African and South Asian origin.

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?

We found that $^{123}$I-MIBG SPECT-CT and $^{18}$F-FDG PET-CT identified the same anatomical regions as active brown adipose tissue (Chapter 5). Moreover, when the $^{123}$I-MIBG SPECT-CT was performed 24 hours after $^{123}$I-MIBG administration, the magnitude of brown adipose tissue activity measured with these techniques correlated strongly. These findings support that brown adipose tissue 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 brown adipose tissue.
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?

There was no difference in brown adipose tissue activity or the sympathetic stimulation of brown adipose tissue between those of European and South Asian origin (Chapter 6). Furthermore, we observed no ethnic differences in other factors influencing brown adipose tissue activity.

PART III: The effectiveness of preventive and therapeutic strategies

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

We found that the lifestyle intervention did not effectively change the weight status, glucose metabolism, blood pressure, or lipid profile in the South Asian target population. After 1 year of follow-up, the metabolic risk factors of the intervention and control groups were similar (Chapter 7). The adherence to the intervention did not explain the lack of change in weight and metabolic profile in the intervention group.

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)?

We observed that patients from European origin lost more weight one year after surgery than patients from African origin, regardless of the type of bariatric surgery (Chapter 8). Furthermore, while based on limited data, our meta-analysis suggested that despite the difference in weight loss, there were no statistically significant differences in remission of type 2 diabetes between these ethnic groups after surgery.

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

We found that African, South-Asian, Turkish and Moroccan patients all had lost less weight one year after gastric bypass surgery when compared to their ethnic Dutch counterparts (Chapter 9). These ethnic differences remained after adjustment for factors that are known to influence post-surgical weight loss, such as baseline BMI and age.
Methodological Considerations

Each individual study in this thesis includes a section that discusses the specific limitations related to the analyzed data. However, before discussing the implications of the main findings of this thesis, some general methodological issues need to be addressed.

The studies included in this thesis were performed in many different populations, varying from young and healthy male volunteers to morbidly obese patients undergoing bariatric surgery. Although these studies differed greatly from one another in terms of their design and outcome measures, most of them were observational by nature. As is the case with all study designs, the use of observational studies has some disadvantages. For example, in a cross-sectional observational study, such as our study on the association between physical inactivity and type 2 diabetes in different ethnic groups, the primary limitation is that the exposure (i.e. physical inactivity) and outcome (i.e. type 2 diabetes) are simultaneously assessed. This could have biased our results through behavioural factors if getting a diagnosis of type 2 diabetes led to an increase of physical activity level, and could therefore have resulted in underestimation of the contribution of physical inactivity to type 2 diabetes. In addition, longitudinal observational studies are often affected by loss to follow-up. For example, in our study on ethnic differences in the association between baseline IFG and FPG with the 10-year incidence of type 2 diabetes, we found that those lost to follow-up had a higher BMI, a greater waist circumference, and a higher prevalence of baseline IFG than those with follow-up data available. Therefore, it is likely that the loss to follow-up resulted in an underestimation of the cumulative incidence of type 2 diabetes that we found in this study. However, the patterns of loss to follow-up were similar across the ethnic groups. Therefore, we find it unlikely that the loss to follow-up affected the differences found between the ethnic groups. Another issue that should be considered is that, in retrospective observational studies, the control of the investigator over data collection is limited. Therefore, information on certain factors that may have influenced the study outcome may be limited. For example, in our studies on ethnic differences in weight loss after bariatric surgery, we reported that patients of European origin lose more weight than patients from other ethnic backgrounds. These ethnic differences remained after adjustment for factors that are known to influence post-surgical weight loss, such as baseline BMI and age. However, it is likely that other unmeasured factors, such as socioeconomic or cultural factors, also contributed to the ethnic differences we found. Because of the retrospective study design and the fact that the data were collected from many different hospitals, we were not able to obtain uniform, comparable data on socioeconomic status and cultural factors. Therefore, it remains speculative how the inclusion of these factors in our analyses would have influenced our results.
Another methodological issue that should be considered is the definition of ethnicity in this thesis. There is a lack of an agreed upon definition of ethnicity. As mentioned in the introduction of this thesis, current definitions all have in common that 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. The way this complex concept of ethnicity is translated into statistical indicators differs between European countries. In the vast majority of the studies included in this thesis (Chapters 3-7), ethnicity was assessed according to self-identified ethnicity, together with the country of birth of the participants and their parents. This rather broad classification of people does not entirely capture the complex concept of ethnicity and inevitably results in heterogeneity within ethnic groups. For example, there may have been differences in language, religion, migration history and culture between the participants who were classified into the same ethnic group in this thesis. The extent to which such differences have contributed to the reported effects of ethnicity on the various outcomes in this thesis remains speculative. Future studies should incorporate more detailed information on this kind of background variables in order to better understand the increased risk of DM in specific ethnic groups.

All individuals from South Asian or African origin that participated in the studies included in the thesis were residing in the Netherlands (with the exception of the patients included in our meta-analysis in Chapter 8). It is important to realize that the prevalence of diabetes among individuals from African or South Asian descent living in industrialized countries is much higher than in those who remained in their countries of origin (1-3). This higher prevalence following migration has been largely attributed to transition to an industrialized lifestyle, which is associated with most known risk factors for diabetes (1,3). Furthermore, studies examining ethnic minority populations living in different industrialized countries have also shown substantial variations in the risk of type 2 diabetes (4,5). For example, South Asian and African ethnic minorities in the Netherlands have higher diabetes rates than their counterparts living in England. The explanations for these differences are not clear, although differences between these groups in diet, early life experiences, physical activity and socioeconomic position have been suggested to play a role (4). Keeping this in mind, caution must be applied when extrapolating the results of the ethnic groups studied in this thesis to groups with the same ethnic background living in different environments and countries.
Implications of the main findings and future directions

**Ethnic differences in the pathogenesis of type 2 diabetes**

As mentioned earlier, the ethnic differences in both the prevalence and incidence of type 2 diabetes may partly be explained by an ethnic difference in the susceptibility to specific risk factors. The differences we found in the association of both impaired fasting glucose (IFG) and physical inactivity with type 2 diabetes between those of South Asian, African and European origin (Chapter 3 and Chapter 4 respectively) suggests an ethnic difference in the pathogenesis of type 2 diabetes. For example, our observation that the association of IFG with the 10-year incidence of type 2 diabetes was stronger among those from South Asian and African origin than among those from European origin may reflect an ethnic difference in the conversion rate from IFG to type 2 diabetes. As it is well known that insulin resistance and beta-cell dysfunction are the two principal components involved in the pathophysiology of type 2 diabetes (6,7), this ethnic difference may be the result of either an ethnic disparity in progression of insulin resistance, or an ethnic disparity in progression of beta-cell failure, or a combination of the two. As weight gain is one of the most important causes in the development of insulin resistance and our findings remained after adjusting for change in weight over time in our study (6,7), we hypothesize that a faster progression of beta-cell failure is likely to be a predominant factor in the rapid conversion rate of IFG to type 2 diabetes in the South Asian and African individuals.

In addition, our finding that the association of physical inactivity with type 2 diabetes appeared stronger in those of European origin than in those from African and South Asian origin could imply that the development of diabetes is less susceptible to the protective effect of physical activity in certain ethnic groups than in others. This may be the result of a difference in pathogenesis as well. For example, insulin resistance might be predominantly determined by environmental factors in those from European origin, and by genetic factors (i.e. non-modifiable factors) in those from South Asian or African origin. However, as our results were based on cross-sectional data and information on the underlying mechanisms (i.e. genetic or environmental factors) was not available in our study, this remains speculative.

So what are the implications of these findings for practice and further research? First of all, given the high incidence of type 2 diabetes among South Asians and Africans with IFG, more frequent testing for type 2 diabetes in prediabetic individuals from these ethnic backgrounds is warranted. At the same time, particularly in South Asians, the risk of type 2 diabetes associated with IFG seems so high that more aggressive preventive approaches may be necessary. One of these approaches may be a lower threshold for starting pharmacological treatment of prediabetes in South Asians. According to American Diabetes Association recommendations, only individuals with both IFG and IGT and one additional risk factor
(age <60 years, BMI ≥35 kg/m2, family history of diabetes in first-degree relative, elevated triglycerides, reduced HDL cholesterol, or A1C >6.0%) should be considered for treatment with metformin, in addition to lifestyle modification (8). However, it has been reported that metformin by itself effectively prevents type 2 diabetes in South Asians with isolated IGT (9). It is unknown whether this is also the case for those with isolated IFG. We recommend that further studies determine whether treatment with metformin in South Asians with isolated IFG effectively prevents diabetes and if so, whether this prevention leads to long-term benefits in diabetes related complications.

What are the implications of our findings on ethnicity and brown adipose tissue (BAT)? As mentioned, we found that BAT activity during cold exposure was similar in individuals from South Asian and European origin (Chapter 6). This was unexpected, as both the tendency of South Asians to develop abdominal obesity and type 2 diabetes (10-12) and the ontogenetic superfluity of the presence of BAT in the warm Indian sub-continent suggested that BAT activity would be lower in South Asians than in those from European origin. As the visualization of BAT activity in humans by means of nuclear medicine techniques is rather expensive and invasive, the results of studies on BAT activity during cold-exposure, such as our studies, are based on small sample sizes. Because of this, caution must be applied when extrapolating these results to South Asian populations in general. Having said that, our findings suggest that BAT might not play an important role in the excessive risk of metabolic disturbances in populations of South-Asian origin. In other words, our results do not identify a low BAT activity as a new risk factor for the high risk of metabolic disturbances in this group. Still, our finding that BAT was present and highly physiologically active during cold-exposure in the South Asians in our study is important, as it suggests that BAT may eventually be used as an additional target to fight metabolic disturbances in South Asians in the future. In fact, the stimulation of BAT activity might be especially important in these and other high risk individuals, given the fact that the current strategies to prevent type 2 diabetes have shown to be rather cumbersome (13,14). At this point however, it is not feasible yet to properly stimulate brown adipose tissue in humans in a way that is applicable for daily life (i.e. without constant cold-exposure or the use of medication that may have undesirable long-term side effects). Therefore, future studies not only need to reveal the exact working mechanism of BAT, but should also focus on appropriate ways to actually influence BAT activity in daily life.

**The effectiveness of preventive and therapeutic strategies in different ethnic groups**

We did not find an effect of a culturally targeted lifestyle intervention in South Asians with a high risk of developing type 2 diabetes in general practice (Chapter 7). This lifestyle intervention, which consisted of individual lifestyle counselling, a family session, cooking classes, and supervised physical activity programme, did neither result in improvement of weight
status nor in a better metabolic profile. Our results were in line with results from studies that have investigated the effectiveness in clinical practice of lifestyle interventions for the prevention of type 2 diabetes among other ethnic groups. Still, our results were somewhat unexpected. As South Asians are known to have a high a-priori risk of developing type 2 diabetes and have a familial disposition toward type 2 diabetes (11), we had expected a high level of awareness and motivation to make behavioural changes, especially during a lifestyle intervention trial. Indeed, participants in focus group interviews carried out before the start of the trial pointed out the necessity of such an intervention for this population. In addition, the intervention in our study was targeted extensively to a population of South Asian origin (15), and the dieticians who performed the individual lifestyle counselling were all trained according to recommended protocols and instructed to monitor the participation of all those included in the study. For these reasons, it came as a surprise that we found neither changes in metabolic profile over time within the control and intervention groups, nor a difference in change over time between these groups. Thus, we believe that understanding the effects of motivational factors and behavioural changes, as well as a detailed process evaluation of the experiences in practice, will be of the utmost importance.

It should be mentioned that, although the lifestyle intervention was not effective in our overall population, we did find that participants who achieved a relatively large weight loss after 1 year (i.e. those within the highest quartile of weight loss) showed more improvement in lipid profile and glucose metabolism than participants in the lowest quartile of weight loss, independently of their group assignment. This emphasises that, if high-risk individuals in this population lose weight, there is a potential health gain. At the same time, the low initial response rate and laborious recruitment (15), the high drop-out rate, and the lack of effect of the lifestyle intervention on weight change and other metabolic parameters raise the question whether our strategy is the optimal approach to prevent type 2 diabetes in the target population. Indeed, the disappointing lifestyle intervention results, together with the extraordinarily high risk of type 2 diabetes in South Asians with prediabetes, suggest that merely fighting already existing metabolic disturbances is not the best option to prevent type 2 diabetes in this population. Additional emphasis should lie on avoiding the development of these metabolic disturbances in the first place by means of prevention strategies in an earlier stage (16). Given the extraordinarily strong association between metabolic disturbances and obesity in South Asians (10), the first priority of such strategies should be the maintenance of healthy weight and obesity prevention. This implies the counselling of all South Asian individuals who are overweight, regardless of their blood glucose value and age, to lose weight and to exercise. Furthermore, education about a healthy lifestyle and the development of obesity and diabetes should start at a young age, for example by means of school-based meetings and exercise programs. Having said that, the high risk of diabetes in South Asians may not be fully attributable to traditional risk factors, such as obesity and
lifestyle related factors. Therefore, apart from avoiding the development of metabolic disturbances, future studies should stay focused on further identifying the exact mechanisms underlying the excessive diabetes risk of South Asians.

The results of this thesis underscore that when it comes to assessing a patients’ risk of type 2 diabetes, or developing preventive strategies for type 2 diabetes, the actual strategy should be targeted to specific ethnic groups. However, is this also the case for certain therapeutic strategies? In Chapter 8 and Chapter 9, we focused on the effectiveness of the most drastic therapeutic option available, namely bariatric surgery, in different ethnic groups. Our results underscored that ethnic differences in weight loss after bariatric surgery are not limited to those between patients of European and African origin (Chapter 8), but extend to other ethnic groups as well (Chapter 9). Specifically, our retrospective data showed that patients from all main ethnic groups in the Netherlands (i.e. Turkish, Moroccan, African and South Asian patients) lost less weight loss than the ethnic Dutch patients. It is important to realize that our results do not imply that the effectiveness of bariatric surgery for morbidly obese individuals in these minority groups should be questioned. In fact, the mean percentage excess weight loss in all ethnic groups in our studies was higher than 50% (which is the threshold considered for ‘successful’ postsurgical weight loss) (17). Therefore, the results of our studies merely show that, at this point, different weight loss results may be expected depending on a patients’ ethnic background. Furthermore, the metabolic consequences of these ethnic differences in post-surgical weight loss are unclear. We found that there was no ethnic difference between patients from African and European origin in post-surgical type 2 diabetes remission despite a lower amount of weight loss in the patients of African origin. This suggests that the metabolical significance of the ethnic differences in post-surgical weight loss may be limited. However, as only three studies in our meta analysis reported on diabetes remission in both African and European patients, our data on post-surgical diabetes remission were very scarce. Therefore, prospective studies should determine whether the ethnic differences in weight loss actually result in long-term differences in remission of co-morbidities or mortality rate.

Despite the fact that the mean excess weight loss was higher than 50% in all ethnic groups, our findings on ethnic differences in post-surgical weight loss demand an explanation. In the studies included in our meta-analysis, biological, psychological, genetic and socioeconomic factors have all been suggested to contribute (18-20). For example, it has been reported that white Americans have shown greater improvement in energy-expenditure in response to weight loss than African Americans, suggesting decreased weight loss efficiency among the latter (18). Other explanations mentioned include that, in the USA, those of African origin usually have lower socioeconomic backgrounds than white Americans, which is known to be associated with obesity and which might also partly explain ethnic differences in post-
surgical weight loss (18,21,22). A possible explanation for our finding that Turkish, Moroccan, African and South Asian all achieved a lower amount of weight loss than their ethnic Dutch counterparts, might be that there were differences in the efficacy of post-surgical programs between these ethnic groups. This may for instance be the result of language problems or lack of culturally adapted lifestyle advice. However, as we were not able to obtain uniform, comparable data on cultural factors and the post-surgical care in our studies, this remains speculative. In future prospective studies, socio-economic, cultural and biological factors should be all taken into consideration to properly determine the exact mechanisms behind the ethnic differences in post-surgical weight loss.

Conclusion
This thesis underscores 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 and 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 from 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 the development of obesity and diabetes should be started as early as possible during childhood.
Reference List


