May 31.2018: WP6: Deliverable 6.3

Final report **WP6** "Identification of specific dietary components that influence the high risk of T2D in South Asian origin people living in Europe by considering current dietary recommendations, and by further investigating novel mechanisms in the relation between diet and T2D in these populations."

Funded by the Health Programme 2014-2020 from the European Union Grant number 664609 HP-PJ-2014 (InPreSD - Innovative Prevention Strategies for type 2 Diabetes in South Asians Living in Europe)

Background

Type 2 diabetes (T2D) occurs more frequently in people from South Asian origin than in those from European origin, both in the country of origin and after migration [1-3]. Furthermore, South Asians develop T2D at younger age and lower body mass index (BMI) than Europeans [4, 5]. Not only do South Asians develop T2D more often, they also have high morbidity and mortality from T2D and related complications. Therefore, South Asians were specifically targeted in interventions to prevent development of T2D in this high risk population [6, 7]. However, results of T2D interventions among South Asians conducted in Europe seemed more modest than those conducted among Europeans.

Diet and physical activity are key modifiable risk factors for T2D [8] and specific recommendations regarding diet and physical activity may be used to prevent or delay the onset of T2D. Such recommendations were for instance used in the DHIAAN and PODOSA interventions [6, 7]. However, remained unknown whether recommendations made regarding diet and physical activity were appropriate for South Asian populations. The recommendations might not be targeted enough to the needs of South Asian populations, as people from South Asian origin have their own characteristics. There is for instance some evidence to suggest that specific changes needed in diet or physical activity may be different in South Asian origin population than in those of European origin [9, 10]. For instance, a difference in association between duration of physical activity and cardio-metabolic risk factors between South Asian and European men and women was found [10].

Besides aforementioned differences in effects of physical activity, differences in the effect of a high-calorie, high-fat diet where found on insulin sensitivity in men [9]. Another study suggested that associations between fatty acids and markers of insulin resistance differ across ethnic groups of Caucasian, East Asian and South Asian origin living in Canada [11]. This may imply that a less healthy diet is more detrimental for the health of South Asian than for Europeans. And a novel target for dietary recommendations may therefore be related to dietary fat intake.

Excess energy and dietary fat intake may result in disturbances in the lipid metabolism. Excess energy intake may lead to disturbances of the long-chain fatty acid metabolism and ectopic fatty accumulation. Lipotoxicity is one of the novel mechanisms suggested to play a role in the pathophysiology of T2D. Markers of lipotoxicity include acylcarnitines and sphingolipids. Where acylcarnitines mark the disturbed long-chain fatty acid metabolism, sphingolipids are produced in non-oxidative pathways and may trigger apoptosis of pancreatic β-cells and distort signalling pathways involved in glucose metabolism.

In order to ultimately identify dietary components to reduce the high risk of T2D in South Asian origin people living in Europe, current recommendations and further novel mechanisms in the relation between diet and T2D were investigated. Specifically, WP6 set out to answers the following research questions: 1. How appropriate are the dietary goals* from current recommendations for prevention of T2D, such as those used in the DHIAAN and PODOSA interventions, in South Asians? And 2. What is the association of fat intake and associated lipotoxicity with the risk of T2D in South Asians?

Below we, first describe the methods and then give a summary of the results (with additional information presented in annexes). Finally we draw conclusions from our findings.

**This was expanded to include physical activity goals.*

Design, methods and analysis

WP 6.1: "How appropriate are the dietary and physical activity goals from current recommendations for prevention of T2D, such as those used in the DHIAAN and PODOSA interventions, in South Asians?"

Within WP 6.1, several steps were taken to determine whether goals from recommendations for prevention of T2D were appropriate. First a systematic review was undertaken to investigate the current recommendations regarding dietary and physical activity (*WP 6.1a)*. Overviews of current recommendations were provided and the existing evidence for these recommendations were investigated. Because not much evidence was available that showed recommendations to be effective to prevent T2D in South Asian populations, we additionally investigated the association of some of the potential targets with T2D. This included existing recommendations including fruit and vegetable (described in *WP 6.1b)* and increasing muscle strength, of which handgrip strength is a marker (described in *WP 6.1c*). Study designs and methods used to investigate these steps are described below.

WP 6.1a Dietary and physical activity recommendations to prevent type 2 diabetes in South Asian adults: a systematic review.

A systematic search strategy was developed in collaboration with a clinical librarian from the Academic Medical Center in Amsterdam, and included PUBMED, Embase, Cochrane library and Web of Science. The search strategy was restricted by the time span (start of the database to September 2017) and language (abstracts in English). Further details of the methodology used for this work can be found in a published protocol manuscript (Annex 1) [12]. In addition to a description of the study aims, methods, numbers and outcomes, detailed information on the included dietary and physical activity strategies included in the selected papers and guidelines were gathered. This was done following a list of characteristics designed to answer the questions regarding which dietary and physical activity strategies used in intervention studies were shown effective. Data on the recommended strategies, targeting and evidence on effectiveness were extracted. In addition, authors were contacted to obtain any missing information. Recommendations were compared to general guidelines. Effectiveness of strategies was further examined by studying effectiveness of included studies. Overall findings on dietary and physical recommendations were discussed, as well as findings by subgroups.

WP 6.1b Ethnic differences in serum carotenoids and their association with type 2 diabetes within the HELIUS study.

Cross-sectional data from the HELIUS study (Amsterdam, the Netherlands) were used. In total, 1014 participants between 18-70 years old with various ethnic background were included, including 204 participants of European, and 203 participants of South Asian origin. Serum carotenoids, a biomarker for fruit and vegetable intake, were determined. Age-adjusted serum carotenoid concentrations were compared using ANCOVA. Multivariate Cox regression was used to estimate prevalence ratios of the association between serum carotenoid concentrations and T2D. Prevalence ratios of the model adjusted for potential T2D risk factors and the model additionally adjusted for serum carotenoid concentrations were compared to study the contribution of fruit and vegetable intake to the ethnic inequalities in T2D.

WP 6.1c Ethnic differences in handgrip strength and their association with type 2 diabetes within the HELIUS study.

To investigate whether the association between grip strength and diabetes incidence differs by ethnic groups we used data from the HELIUS study, where 4564 participants were from white-Dutch background and 17,553 were from other ethnic-minority groups. Grip strength, which is a good proxy of overall strength, has been previously associated with different health outcomes, but more importantly, the effect of lower grip strength has a worse adverse health effect in non-white populations compare to white-Europeans. In order to test this in the HELIUS study, we first conducted a series of logistic regression to test the association between 5-kg lower grip strength and diabetes in white-Dutch and non-white ethnic minority populations. Then, these analyses were replicated using incidence diabetes data collected from insurance companies in the Netherlands. Cox-regression analyses were used to estimate the hazard and their 95% CI.

WP 6.2: What is the association of lipid intake and associated lipotoxicity with the risk of T2D in South Asians?

The investigation of lipid intake and its associated lipotoxicity in South Asians has potential to lead to novel targets to prevent T2D in South Asians. Several steps were undertaken to better understand its role in the pathogenesis of T2D in South Asians. First, the role of lipid intake was investigated (*WP 6.2a)* by investigation of plasma concentrations of *cholesteryl ester fatty acids.* Thereafter, the role of lipotoxicity was investigated (*WP 6.2b-d)* by studying relevant biomarkers. These include acylcarnitines, amino acids and sphingolipids, reflective of a disturbed long chain fatty acid metabolism, disturbed amino acid metabolism and increased use of non-oxidative pathways. We first investigated whether ethnic differences in these concentrations occurred from a younger age or increased with age (*WP 6.2b)*. We then investigated the association of these metabolites with incident T2D (*WP 6.2c-d)*. Moreover, because lipotoxicity may also lead to inflammation, a possible explanation for the observed differences in prevalence of T2D may lie in an earlier inflammation of adipose tissue in South Asians than in Europeans. We, therefore, investigated ethnic differences in inflammation as well (*WP 6.2e)*. Study designs and methods used to investigate these steps are described below.

WP 6.2a Do plasma cholesteryl ester fatty acids mediate the association of ethnicity with type 2 diabetes?

Cross-sectional data from the HELIUS study were used. 1042 participants between 18-70 years old with various ethnic background were included, including 202 participants from European, and 206 participants from South Asian origin. Plasma cholesteryl ester fatty acids (CEFA) were determined as a biomarker for dietary lipid intake in the past weeks. Ethnic differences in plasma CEFA levels are determined by multiple linear regression. Logistic regression is used to determine the associations between plasma CEFA and T2D. Interaction terms are used to determine whether associations differed by sex and ethnic groups. Mediation analysis is used to identify whether CEFA contributed to the association between ethnicity and T2D. All analyses were adjusted for age, sex, smoking, physical activity, and BMI, and where appropriate ethnicity. More detailed methods are described in Annex 7 and the published article [13].

WP 6.2b The association of acylcarnitines and amino acids with age in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands

Acylcarnitines and amino acid concentrations were measured in a random subsample of 350 European and 350 South Asian origin participants from the HELIUS study (Amsterdam, The Netherlands). Principle components from the metabolites are derived by principle component analysis. These principle components are characterized as the primary outcome. In addition individual acylcarnitines, amino acids, and ratios of acylcarnitines are explored. Linear regression is used to assess ethnic differences in metabolite concentrations, and their age-trends. All models are adjusted for BMI, and additionally for energy and lipid intake in sensitivity analyses. The detailed methods are described in Annex 8.

WP 6.2c The association of acylcarnitines and amino acids with T2D incidence

A case-cohort study was done to investigate the association with T2D incidence of acylcarnitines and amino acid concentrations were measured in a random subsample of 350 European and 350 South Asian origin participants from the HELIUS study (Amsterdam, The Netherlands). Additionally, metabolites were measured for participants not included in the reference cohort with incident T2D as determined by deterministic linkage with insurance data. We determined hazard ratios by Weighted Cox proportional hazard regression models using Prentice weighting to account for the case-cohort design. The interaction between metabolites and ethnicity with incident T2D as the outcome was checked. All analyses were adjusted for sex, age, smoking, physical activity, BMI and waist circumference.

WP 6.2d The association of sphingolipids with T2D incidence

In the same case-cohort study as described under *WP 6.3.c* sphingolipids were measured for a random subsample of 350 Europeans, 350 South Asians and for participants with incident T2D. Ethnic differences in sphingolipids were determined by multiple linear regression. The analyses of associations with T2D will be done Weighted Cox proportional hazard regression models. These are underway.

WP 6.2e CRP mediates ethnic differences in type 2 diabetes: results from the HELIUS study

Cross-sectional data from the HELIUS study were used. 5998 participants between 18-70 years old with various ethnic background were included, including 1000 participants from European, and 999 participants from South Asian origin. In addition incident T2D was determined from data linkage with insurance companies. C-reactive protein was used as a marker of inflammation. Differences in CRP levels between ethnic groups were determined by multivariate linear regression. The association of CRP with both prevalent and incident T2D was determined by logistic regression, and it was checked whether the strength of the association differed by ethnicity by using an interaction term. Mediation analysis was used to identify whether CRP contributed to the association between ethnicity and T2D. All analyses were stratified by sex and were adjusted for age, physical activity, smoking, body mass index (BMI) and waist circumference (WC).

Results

WP 6.1a Dietary and physical activity recommendations to prevent type 2 diabetes in South Asian adults: a systematic review.

In a systematic review, we investigated how appropriate current dietary and physical activity recommendations were to prevent type 2 diabetes in South Asians. The systematic search for scientific literature regarding dietary and physical activity recommendations to prevent T2D among South Asian adults, resulted in the final inclusion of eighteen intervention studies and four guidelines. More detailed information about results of WP 6.1a can be found in Annex 4. We found that included strategies in these intervention studies and guidelines were largely in line with existing guidelines for the general population. Strategies, for instance, included recommendations on sugar intake, vegetables and fruits, and on the duration of activity per week. The included strategies were often based on prior T2D intervention studies in the general population, or on general population guidelines from the geographical area where the study was conducted. No evidence was given that supports the effectiveness of components included in the intervention for South Asian populations in particular. It was not possible to draw conclusions on effectiveness of included components based on comparisons of studies, as the number of studies we identified was limited and included components within studies overlapped. In conclusion, our review confirmed that existing dietary and physical activity guidelines were not supported by evidence on their specific effectiveness for prevention of T2D in South Asians.

WP 6.1b Ethnic differences in serum carotenoids and their association with type 2 diabetes within the HELIUS study.

Recommendations that are often made include dietary strategies regarding vegetables and fruits. To investigate whether these recommendations might be useful in South Asians, a biomarker (carotenoids) for dietary intake of fruits and vegetables was investigated. More detailed information about the results can be found in Annex 2. It was found that age-adjusted serum carotenoid concentrations were higher among European origin participants than among South Asian origin participants. Furthermore, serum concentrations of total carotenoids, α-carotene, β-carotene and β-cryptoxanthin were inversely associated with prevalent T2D. These associations were robust by sex and ethnicity. However, differences in serum carotenoid concentrations did not explain ethnic inequalities in prevalence of T2D. We can therefore conclude that recommendations regarding dietary intake of fruits and vegetables may be suitable to prevent T2D in European as well as South Asians. The fruit and vegetable intake may have to be augmented if the aim is to resolve ethnic differences in T2D prevalence.

WP 6.1c Ethnic differences in handgrip strength and their association with type 2 diabetes within the HELIUS study.

A new recommendation to be added to prevent T2D could be related to muscle strength. Therefore, handgrip strength was studied in various ethnic groups. The distribution of grip strength across different ethnic groups was tested using density probability plots. In summary, these analyses revealed that South Asians and other non-White ethnic minority groups have lower levels of grip strength compared with white-Dutch participants. The distribution curve was shifted to the left for both men and women, suggesting that the overall distribution of grip strength for men and women of non-white ethnic background is lower compared to white-Dutch population. A graph of the distributions is shown

in Annex 3. When the analyses were stratified by ethnicity, the white-Dutch population had a 17% higher odds of diabetes by 5-kg lower grip strength compared to non-white ethnic minority groups who had a 13% higher odds for diabetes. These associations were independent of major confounding factors (age, sex, diet, body weight, height and socio-demographic factors).When these analyses were replicated using diabetes incidence (202 diabetes cases were identified over a 4-5 years follow-up). These analyses showed that white-Dutch population had a 72% higher risk of developing diabetes per 5-kg lower grip strength, whereas the risk for non-white ethnic minorities, including South Asians, was 19% higher per 5-kg reduction in grip strength. These results were independent of major confounding factors. For the overall population, 5-kg lower grip strength was associated with a 15% higher odds for diabetes (OR: 1.15 [95%CI: 1.09; 1.21], p<0.0001). When diabetes incidence was used as an outcome we found that 5kg-lower grip strength was associated with a 14% higher hazard for diabetes (HR: 1.14 [1.00; 1.31], p=0.050). These results were independent of major confounding factors.

WP 6.2a Do plasma cholesteryl ester fatty acids mediate the association of ethnicity with type 2 diabetes?

Investigation of fat intake and ensuing lipotoxicity may potentially lead to novel targets for dietary recommendations to prevent T2D in South Asians. Therefore, we ,first, investigated differences in fat intake between ethnic groups. Then, we investigated whether fat intake may mediate ethnic differences in T2D. More detailed information regarding the results can be found in Annex 7 and in the published article [13]. We found that the percentage of saturated fatty acids of the total concentration and the percentage of mono-unsaturated fatty acids of the total concentration were higher among participants of European origin than those of South Asian origin, while the percentage of polyunsaturated fatty acids was higher among those of South Asian origin. The associations of CEFA with T2D showed similar directions across both ethnic groups. T2D was statistically significantly, positively associated with the total amount of saturated fatty acids, and negatively with the total amount of polyunsaturated fatty acids. The differences in prevalence of T2D between those of European and those of South Asian origin were not mediated by differences in plasma CEFA. We concluded, recommendations regarding fatty acids may be beneficial to prevent T2D; the more favourable patterns should be kept.

WP 6.2b The association of acylcarnitines and amino acids with age in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands

After investigating the markers of dietary fat intake, we studied biomarkers reflecting lipotoxicity. These included acylcarnitines, sphingolipids and, additionally, amino acids. Because of the observed lower age at onset of T2D, we not only studied the differences in concentrations, but also age trends of acylcarnitines and amino acids in Europeans and South Asians. We found that, in general, concentrations of metabolites were higher among South Asians than Europeans. Specifically, amino acids in women and both amino acids and acylcarnitines in men. Further, the metabolite concentrations increased with age, similarly in both South Asians and Europeans. This suggests that the fatty acid and amino acid metabolism are more dysregulated among South Asians compared to Europeans from a young age. During adulthood disruption of fatty acid and amino acid metabolism increases, although similarly in both ethnic groups. Details of this study can be found in Annex 8. The next step was therefore to identify the association of acylcarnitines and amino acids with T2D in South Asians and Europeans.

WP 6.2c The association of acylcarnitines and amino acids with T2D incidence

We found that higher levels of amino acids were positively associated with incident T2D while higher levels of acylcarnitines were associated with a lower incidence of T2D. This association was similar in both ethnic groups. A table of the associations is shown in Annex 7. The previously identified higher levels of mainly amino acids at a similar age, therefore, suggests that lipotoxicity may indeed be a potential explanation for the observed ethnic differences in T2D prevalence and incidence. In the next step another biomarker (sphingolipids) of lipotoxicity was studied.

WP 6.2d The association of sphingolipids with T2D incidence

We found that most sphingolipid concentrations were lower among South Asians than among Europeans, a table of these ethnic differences is shown in Annex 8. Results of the associations of sphingolipids with incident T2D are underway.

WP 6.2e CRP mediates ethnic differences in type 2 diabetes: results from the HELIUS study

Previous steps showed that lipotoxicity, specifically disruption of the amino acid and fatty acid metabolism, may be an important explanation for ethnic differences in prevalence and incidence of T2D. The next step is to identify by which mechanisms this leads to T2D. One of the proposed mechanisms is the stimulation of inflammatory pathways. In *WP 6.3* we, therefore, studied low-grade inflammation with the biomarker CRP. More detailed results can be found in Annex 10. We observed that CRP levels, marking low-grade inflammation, were higher among those of South Asian origin than those of Dutch origin. A positive association between CRP and T2D was found, which was similar across ethnic groups. The association, however, was almost fully attenuated when adjusted for measures of adiposity levels. CRP partly mediated ethnic differences in prevalence of T2D between Europeans and South Asians in men, but not in women. This effect was only observed in models unadjusted for adiposity levels. In conclusion, low-grade inflammation may play a role in ethnic differences in the prevalence and incidence of T2D. This is however largely related to differences in adiposity levels, while differences in markers of lipotoxicity were independent of adiposity levels. We therefore suggest that other mechanisms are (also) involved in the association between lipotoxicity and T2D.

Conclusions

WP6 aimed to ultimately identify dietary components that may reduce the risk of T2D in South Asians living in Europe. The analyses done were described in detail above. Below we summarise some of the conclusions from our work.

1. In a systematic review investigating which recommendations were made in existing guidelines and interventions and the evidence for their effectiveness, we showed that recommendations to date have been similar to recommendations for the general population. Moreover, the goals in current recommendations were not based on evidence that showed these goals to be effective to prevent T2D in populations of South Asian origin and no evidence could be identified. Therefore, our recommendation is that evaluation of current and emerging components among South Asian populations is done to formulate more specific recommendations in future intervention studies and guidelines.

2. In the current project and other recent work, we have evaluated the role of some of the conventional strategies from current guidelines. First, the investigations of fruit and vegetable intake in the current study showed that associations with the prevalence or incidence of T2D was similar among South Asians, suggesting that higher intakes of fruit and vegetables may prevent T2D both in South Asians and Europeans. We, therefore, suggest that dietary recommendations on fruit and vegetable intake based on recommendations to prevent T2D in the European population are also included for the South Asian population.

   In previous analyses in HELIUS, we investigated the role of sugar consumption with and its role in the unequal burden of T2D prevalence, within a study "western dietary pattern" [Huisman et al. 2018]. This dietary pattern high in sugar and saturated fat was less common among South Asians, not associated with T2D, and did not explain the unequal burden in prevalence of T2D across the ethnic groups. We concluded that, while in general avoidance of this pattern may be beneficial for health (e.g. for depression [Vermeulen et al 2017], strategies focusing on this "western dietary pattern" are not likely to reduce the ethnic inequalities in T2D.

   We also studied the strategies reflecting physical activity. In previous work of members from the EuroDHYAN team showed that South Asian men and women need to undertake approximately 230 minutes of moderate intensity physical activity per week to achieve a health benefit. This equates to South Asians undertaking an extra 10-15 minutes of moderate intensity physical activity per day on top of existing recommendations [10]. In the present study we add to that, that South Asians may also particularly benefit from strength exercise as grip strength is lower than among Europeans and was more strongly associated with T2D.

3. Furthermore, we studied evidence for recommendations on fat intake. Previous work has shown that differences in the amount and type of lipids in the diet may be associated with insulin resistance and T2D. For instance, a high-calorie, high-fat diet impaired insulin sensitivity in South Asian men, but not in White European men [9], suggesting that this dietary component might be a potential entry point to increase the effectiveness of dietary recommendations in South Asians. In the present project, we found that the plasma levels of saturated, unsaturated and polyunsaturated CEFA differed between the ethnic groups and

were associated with T2D, independently of the total reported energy intake. Yet, these differences did not explain the ethnic difference in diabetes burden, mainly because levels were more advantageous among South Asians. This lack power to explain differences in T2D confirms the aforementioned analyses of the high-fat high-sugar "western dietary pattern" [Huisman 2018]. This leads us to conclude that, while a focus on fat intake may not reduce inequalities, the maintenance of the more favourable lipid profile should be encouraged in order to prevent a further increase of the T2D risk in South Asians.

4. Besides the fat intake and lipid profile, we also evaluated markers of dysfunction of the long-chain fatty acid metabolism. Despite the aforementioned more favourable lipid profile, metabolite levels reflective of a dysfunctional long-chain fatty acid metabolism were consistently less advantageous among South-Asian Surinamese than among Dutch participants without diabetes from a young age, although similar increases were observed by age. These patterns in metabolite levels seem in line with the observation that type 2 diabetes occurs more frequently from a younger age in South-Asians than Europeans. In further analyses, we confirmed that these metabolites were indeed associated with diabetes incidence. We, therefore, conclude that disruption of this metabolism plays a role in the observed ethnic differences in T2D. It is, however, still uncertain why the lipid and amino acid metabolism is more disrupted in South Asians than in Europeans. This should be subject of further study.

5. The relevance and effects of recommendations may differ between subgroups within the population. The occurrence of T2D has, for instance, been shown to differ between men and women. In the present study, we did not find consistent differences in both the dietary components as well as the associations of these components with T2D by sex. Moreover, the presence of absence of overweight may be relevant. Among those without overweight, intervention may unnecessarily delayed. Previous trials of lifestyle intervention have mostly focused on populations with overweight. However, this strategy may miss a substantial proportion of those at risk, as in South Asian origin population T2D may already occur at a lower body weight than in other populations. In a recent analysis in another project, we indeed found a higher prevalence of metabolically unhealthy normal weight, including elevated glucose, in South Asians than in other ethnic groups [Perini et al., submitted]. In the current study, we found no evidence to support a different association of components by body weight [additional analyses not shown]. This particularly relevant, as it confirms the finding of our IPD meta-analysis [Jenum et al, in preparation] suggesting that behavioural intervention may be used among the whole population; the analyses did not provide evidence for a difference in potential effectiveness of behavioural interventions by sex and between those with a BMI above or below 27.5 kg/m2.

Published papers

M Muilwijk et al. Dietary and physical activity strategies to prevent type 2 diabetes in South Asian adults: protocol for a systematic review. [doi: 10.1136/bmjopen-2016-012783]

M Muilwijk et al. Plasma cholesteryl ester fatty acids do not mediate the association of ethnicity with type 2 diabetes: results from the HELIUS study [DOI: 10.1002/mnfr.201700528]

Forthcoming papers

M Muilwijk et al. Dietary and physical activity recommendations to prevent type 2 diabetes in South Asian adults: a systematic review. [submitted for publication]

M Flores Sanchez et al. Ethnic differences in serum carotenoids and their association with type 2 diabetes within the HELIUS study.[submitted for publication]

C Celis et al.Ethnic differences in handgrip strength and their association with type 2 diabetes within the HELIUS study. [in preparation]

M Muilwijk et al. The association of acylcarnitines and amino acids with age in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands [submitted for publication]

M Muilwijk et al. The association of acylcarnitines and amino acids with T2D incidence in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands [in preparation]

M Muilwijk et al. The association of sphingolipids and amino acids with T2D incidence in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands [in preparation]

M Muilwijk et al. CRP mediates ethnic differences in type 2 diabetes: results from the HELIUS study [submitted for publication]

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Annex 1. EuroDHYAN WP 6.1a

[published as BMJ Open 2017;7:e012783. doi: 10.1136/bmjopen-2016-012783]

Dietary and physical activity strategies to prevent type 2 diabetes in South Asian adults: protocol for a systematic review

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Abstract

Introduction Type 2 diabetes (T2D) is a major health concern among populations of South Asian ethnicity. Although dietary and physical activity interventions may reduce the risk of T2D, the effectiveness has been moderate among South Asians. This might (in part) be because this subgroup follows strategies that were originally developed for interventions among other populations. Therefore, this review aims to assess the evidence for the current dietary and physical activity strategies recommended in T2D prevention intervention studies and guidelines for South Asians.

Methods and analysis Included will be all studies and guidelines on dietary and/or physical activity strategies to prevent T2D in adult South Asians. Two reviewers will search online databases from their start until the present date for published and unpublished experimental/quasiexperimental studies, with at least an abstract in English. References of identified articles and key reviews will be screened for additional studies. Guidelines will be identified by searches in online databases and websites of public organisations. Finally, expert consultations will be held to supplement any missing information. Trial quality will be assessed with the Quality Assessment Tool for Quantitative Studies Data, and guidelines with the Appraisal of Guidelines for Research & Evaluation II. Data on the strategies recommended, targeting and evidence on effectiveness will be extracted by two reviewers and presented in tabular and narrative forms. Recommendations will be compared with the National Institute for Health and Care Excellence guidelines [PH35]. Overall findings on dietary and physical activity recommendations, as well as findings for specific subgroups (eg, by sex), will be discussed.

Ethics and dissemination Ethics assessment is not required. Start date: 1 January 2016, finishing and reporting date 31 July 2016. Results will be published in a peer-reviewed scientific journal, the project report of EuroDHYAN (www.eurodhyan.eu) and in a PhD dissertation.

Trial registration number The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42015027067.

Strengths and limitations of this study

Our extensive strategy to identify relevant studies and guidelines includes searching a large number of online databases, manually searching public health websites and consultations with relevant experts.

Quality assessment and reporting of results will be done in accordance with relevant guidelines of systematic reviews.

Reviewers will not be blinded during quality assessment.

Introduction

Populations of South Asian origin are at particularly high risk for type 2 diabetes (T2D).[1–3] This is of concern because T2D increases the risk of several comorbid conditions including cardiovascular and renal disease, which adversely impacts on quality of life and lifespan.[4] Diet and physical activity are key modifiable risk factors for T2D.[5] It is known that interventions with specific strategies targeting these behaviours may prevent or postpone T2D.[6–8] Strategies for diet and physical activity to prevent T2D have also formed the basis for population-wide prevention guidelines issued by public health organisations. For instance, in the UK, ‘eating fibre-rich foods’ was included in the T2D prevention ‘Population and community-level interventions guideline,’ issued by the National Institute for Health and Care Excellence (NICE).[9]

Recently, interventions targeting diet and physical activity have also been implemented to reduce the risk of T2D among populations of South Asian origin. However, the trials evaluating intensive lifestyle interventions in this group show only moderate effects.[10–13] One interesting observation is that, while the mode of delivery of these interventions was often culturally adapted, the recommended dietary and physical activity strategies were often based on those developed for application in other populations.[10 11] For instance, the intervention implemented in the DHIAAN trial among South Asians in the Netherlands was culturally adapted to that population.[10] However, the adaptations mainly concerned the design of the intervention and the mode of delivery.[14] The strategies for diet and physical activity directly followed those originally developed for the general Dutch population.[14] The use of similar targets may be problematic if the effects of specific changes in physical activity or diet varies across populations; studies suggest that this may be the case.[15 16] For instance, a difference in the effects of a high-calorie, high-fat diet on insulin sensitivity was found between South Asian and Caucasian men.[15]

This raises the question whether the strategies investigated in intervention trials among South Asians to date are entirely appropriate for South Asian populations. While previous reviews have discussed the effects of interventions on the prevention of T2D, for instance by estimating its effects on weight loss, none has examined the specific strategies that were used.[5 12 17 18]

An evaluation of the different strategies will provide an overview of current strategies and their relevance to the South Asian population which will, ultimately, stimulate the development of more targeted and effective preventive strategies.

Therefore, this systematic review will examine the dietary and physical activity strategies recommended in the guidelines of public organisations and in intervention studies for the prevention of T2D in adult South Asian populations.

The specific questions in this review are:

What are the current dietary and physical activity strategies used for the prevention of T2D in adult South Asian populations worldwide?

Were the strategies specifically targeted to characteristics of the South Asian population?

How effective were the strategies for the prevention of T2D in the South Asian population?

This paper describes the protocol that will be used for the systematic review.

Methods and analysis

This systematic review protocol is, where appropriate, in line with the preferred reporting items for systematic review/meta-analysis protocols.[19] The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42015027067.

Design

Systematic review.

Eligibility criteria

We will include intervention studies as well as guidelines. Guidelines are defined as a set of recommended strategies especially developed for the target population. These may include clinical practice guidelines as well as guidelines developed by public organisations, ministries of health, national organisations, primary medical organisations or community-based organisations. Selections of studies as well as guidelines will be based on the following criteria:

Study designs

All intervention studies with experimental/quasiexperimental evaluations will be considered: these include (cluster) randomised controlled trials (RCTs), non-RCTs and before-after studies.

Modelling studies, study protocols, reviews, retrospective cohort studies and cross-sectional studies will be excluded, as they do not report on experimental evaluations of an intervention in a population.

All dietary and physical activity guidelines on the prevention of T2D in South Asians will be included.

Participants

Only studies or guidelines targeting adults aged ≥18 years will be included.

The study population should consist of at least 75% South Asians, or have an identifiable subpopulation of at least 75% South Asian ethnicity (eg, in a stratified sample). South Asian ethnicity is defined as descending from the South Asian subcontinent, that is, the countries Bangladesh, Bhutan, India, Nepal, Pakistan or Sri Lanka. For studies set in the Indian subcontinent, we will assume that the population is South Asian, unless specified otherwise.

Studies on pregnant women or malnourished populations will be excluded, as these groups may require specific interventions.

As the focus of the review is on the prevention of T2D, interventions among populations with T2D are excluded. Studies and guidelines that report on an identifiable subgroup of people without T2D may be considered, for example, in reports combining an investigation of diabetes prevention and management.

Interventions

Of interest are dietary and physical activity interventions at the individual, household or community level that aim to reduce T2D risk.

Studies exclusively on drugs and surgical interventions, or studies on drugs and/or surgical interventions in combination with dietary and/or physical activity interventions will be excluded. However, studies may be included if drugs and surgical interventions are used as alternative interventions or as the comparator in a study on dietary and/or physical activity interventions.

Comparators

All types of comparators will be included, for example, within-group comparisons (before-after study), usual care or alternative interventions, including drugs.

Outcomes of interest

The outcomes of interest include all descriptive data of dietary and physical activity strategies of the included intervention studies and guidelines. For the description of the effectiveness, the outcomes of interest are related to the effects of the intervention on the prevention of T2D. Therefore, we will consider changes in incident T2D, pre-diabetes and underlying measures of glucose metabolism. Reports on the reduction of overweight/obesity are also considered if the intervention ultimately aims to reduce the T2D risk.

Primary outcomes are

dietary strategies to prevent T2D

physical activity strategies to prevent T2D.

Secondary outcomes are

incidence of T2D

incidence of pre-diabetes

indicators of T2D, that is, impaired fasting glucose or impaired glucose tolerance

anthropometric indicators of adiposity.

The outcomes will be collected as reported, and the measures and definitions used to classify the outcomes will be extracted to facilitate interpretation of the reported findings.

Setting

All types of settings (eg, individual, household or community level) in which the intervention was carried out will be included. All geographical locations are considered.

Language

Included will be articles in any language that have an abstract available in English. For full-text papers not available in English, we will translate the methods and results sections. Guidelines written in any language will be included. Manuscripts and guidelines that cannot be translated by a member of the study team will be dealt with on a case-by-case basis.

Time span

A search will be conducted from the start of each database in our search strategy until the present date. This time limit will cover the relevant period, as previous reviews on interventions in South Asian populations indicate that no studies were conducted before the start of the database.[12 17]

Selection based on quality assessment

Studies with a weak rating in the quality assessment will be excluded from the effectiveness assessment. However, studies will be included in the overview of dietary and physical activity strategies regardless of the quality score. This is done because the quality of recommended strategies may be independent from the quality of the conducted study.

Search methods

Scientific literature

The search strategy (see online supplementary appendix 1) was developed in collaboration with a clinical librarian from the Academic Medical Center (Amsterdam) and was peer reviewed by members of the project group of the EuroDHYAN study (www.eurodhyan.eu). Eligible published work will be identified by searching for reports in the following databases: PUBMED, Embase, Cochrane Library and Web of Science.

Unpublished and in-progress studies will be identified by searching the world's largest trial registers, trial registers of the South Asian countries and registers of the top five emigration countries of the South Asian countries with 1 million or more emigrants a year. These trial registers are: WHO International Clinical Trials Registry Platform, International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, ISRCTN Register, EU Clinical Trials Register, the Clinical Trials Register India, the Sri Lanka Clinical Trials Registry, The Saudi Clinical Trials Registry, UK Clinical Trials Gateway and Health Canada's Clinical Trials Database. The search strategy is presented in online supplementary appendix 2. The study leaders of the identified unpublished and in-progress studies will be contacted to establish whether published literature was missed. We will provide an overview of ongoing studies that have not yet published any results.

Additionally, the reference lists of five key reviews[5 12 17 18 20] and of all the included studies will be screened.

Expert consultations will be held to identify any missing studies.

The search strategy is restricted by the time span (start of the database to present) and language (abstract available in English).

Supplementary Material

Supplementary file

[Protocol_Appendix_2_23-5-2016.pdf]

Supplementary Material

Supplementary file

[Protocol_Appendix_1_23-5-2016.pdf]

Guidelines

Two reviewers will electronically search for relevant guidelines in the following databases: the US Guidelines Clearing House, Canadian Medical Association Infobase: Clinical Practice Guidelines Database (CPGs), The Scottish Intercollegiate Guidelines Network, National Health and Medical Research Council: Clinical Practice Guidelines, eGuidelines, International Guideline Library. The search strategy is presented in online supplementary appendix 2.

Other dietary and physical activity guidelines will be identified by online searches of the grey literature. We will search for websites of public organisations on the worldwide level, such as the WHO and the Food and Agriculture Organisation. In addition, websites will be searched of ministries of health and nutrition, nutrition centres, physical activity organisations, primary medical organisations for diabetes and community-based organisations operating at the national, state or province level.

The websites of these organisations will be identified using a publicly available search engine (Google) and visiting web pages of the local government. After identification of the web pages of the various organisations, the individual websites will be searched for the information that is needed by clicking the appropriate headings and/or by use of internal search engines.

Websites that cannot be translated by any of the team members will be handled on a case-by-case basis.

These searches will be conducted in all South Asian countries: Bangladesh, Bhutan, India, Nepal, Sri Lanka and Pakistan. In addition, we will include the top five emigration countries of the South Asian countries with 1 million or more emigrants a year: Saudi Arabia, UK, Kuwait, Oman, USA, United Arab Emirates, Canada and Qatar.[21]

Expert consultations will be held to identify relevant missing guidelines.

Study records

Data management

Citation titles and abstracts will be exported from the search engines to Endnote V.X7.4. Duplicates will be removed automatically and, thereafter, manually checked for any missed duplicates. For citations found eligible during screening of titles and abstracts, we will retrieve full texts and import those into Endnote. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be manually created during the screening process. Guideline titles and summaries will be screened on the websites of the search engines and on other relevant websites. Full-text guidelines will be exported from the search engines and websites to a folder on the personal computers. The source of the guidelines and the date on which the guideline was retrieved will be stored. Duplicates will be removed manually and eligible full-text guidelines will be stored in a separate folder.

Study selection

Two reviewers will independently screen titles and abstracts for eligibility. Discrepancies in screening will be resolved by discussion. A third reviewer will be consulted if no consensus is reached. Full texts will be retrieved for the selected articles, and two reviewers will assess whether these meet the inclusion criteria. Discrepancies will be resolved by discussion and, if no consensus is reached, a third reviewer will be consulted for arbitration. The reasons for exclusion of full texts will be noted.

Guidelines will be selected by two reviewers. Discrepancies in selection will be resolved by discussion and, in case no consensus is reached, a third reviewer will be consulted.

Data extraction

Data will be extracted from the selected papers by two reviewers. Discrepancies will be resolved by consensus, and a third reviewer will be consulted if necessary. In the description of the data, information from records describing the same study ID will be combined. We aim to describe dietary and physical activity recommendations, and the evidence for any targeted advice for the South Asian population.

For identified intervention studies, data will be extracted from the identified reports and also from protocols describing the intervention. Also, a search will be made by study name for protocols published in the medical literature or on study websites. If these are not available, the corresponding authors will be contacted for the intervention protocols. We will register contact attempts and report whether protocols were retrieved. Corresponding authors of the included studies will also be contacted to resolve any ambiguities.

For identified guidelines, the URL and the date of the website visit will be recorded. Data are extracted from the guidelines by two reviewers. Discrepancies are resolved by consensus and, if necessary, a third reviewer is consulted. The primary outcomes are the dietary and physical activity recommendations made. Further, we will examine whether and how recommendations were targeted to the South Asian population, including references that provide evidence for these adaptations.

The following data will be extracted for intervention studies:

study ID; reported study type (eg, RCT and before-after study); geographical setting (country and (sub)urban/rural); setting of the study (eg, household, community-based or individual); included sample size/number of clusters + cluster sizes; relevant demographic characteristics (including age, ethnicity, country of origin, % male and sociodemographic characteristics); description of intervention, type of interventions and exact dietary (grouped by nutrients, products or food patterns) and physical activity interventions; intervention strategy; duration of the intervention; comparator; intended and reported study duration; inclusion/exclusion criteria; primary and secondary aims of the study (eg, weight loss or prevention of T2D); outcomes; effect sizes; confounders adjusted for; bias assessment; follow-up rate and handling of dropouts;

follow-up period; adaptations for South Asian target group; evidence used to underpin the strategies included in the interventions.

The following data will be extracted for guidelines:

organisation name; geographical setting (country); operating level, for example, national or state/province level; description of intervention, type of interventions and exact dietary (grouped by nutrients, products or food patterns) and physical activity interventions; specified subgroups or inclusion/exclusion criteria; dietary (grouped by nutrients, products or food patterns) and physical activity recommendations; adaptations for South Asian target group; evidence used to underpin the strategies included in the guidelines.

Risk of bias

The Quality Assessment Tool for Quantitative Studies[22] (developed by the Effective Public Health Practice Project) will be used for a quality assessment of the included studies.

The reviewers will not be blinded to the studies during the quality assessment process, because it is expected that the reviewers will be familiar with some or all identified studies.

Two reviewers will individually rate the components, which include: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analyses. Each section can be rated strong, moderate or weak.

The overall study will be rated according to the section ratings. No weak ratings will result in a strong study rating, while one weak rating will result in a moderate rating for the study, and two or more weak ratings will result in a weak overall rating.

The quality of guidelines will be assessed by the Appraisal of Guidelines for Research & Evaluation II instrument.

Two reviewers will independently rate the components which include: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Items are scored on a 7-point scale.

For both types of quality assessment methods agreement of reviewers will be checked, in case of disagreement a discussion will be held and, if no consensus is reached, a third reviewer will judge.

If the study quality is judged to be weak, the study results will not be used to assess the effectiveness of the interventions. However, the dietary and physical activity recommendations and evidence base for these recommendations will still be reported.

Data analysis

Synthesis

Data on dietary and physical activity recommendations from the intervention studies and from the guidelines will be presented in tabular and narrative forms to provide an overview of the currently used dietary and physical activity strategies to prevent T2D in adult South Asian populations. The results will be compared with the NICE guidelines [PH35] 'Type 2 diabetes prevention: population and community-level interventions,' published in May 2011.[9] This is the most recent guideline for the prevention of T2D in the general population. Comparing identified strategies with the strategies from the NICE guidelines will enable us to identify to what extent strategies match or deviate from the current insights in strategies that were developed to prevent T2D in the general population. We will identify whether the strategies were specifically targeted to characteristics of the South Asian population, and will describe the available evidence for the effectiveness of these adaptations. This will include reviewing any citations given for evidence on the effectiveness of the recommended changes in relation to the risk of T2D or the glucose metabolism among South Asians. In addition, we will consider any evidence on the effectiveness of (targeted) strategies from the included intervention studies if quality was assessed to be moderate or strong. Finally, we may look for further observational data on the prevalence of the dietary and physical activity strategies and the association of components with T2D in the scientific literature. In addition, in the evaluation of our findings, we will analyse variations in the recommendations by population subgroups. Subgroups can consist of various ethnic groups, migrant/non-migrant groups, geographical setting (Europe/USA/Asia/Oceania), sex (men/women) and/or age (≤50 years/≥50 years).

Amendments

In case of amendments, we will provide the date of each amendment and a description of the change and its rationale in this section. No changes will be incorporated in the protocol. MM will be responsible for approving, documenting and implementing the amendments.

Acknowledgments

The authors thank Faridi S van Etten-Jamaludin, clinical librarian at the Academic Medical Center, for her help with the development of the search strategy for the different databases.

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Footnotes

Contributors Conceptualisation: MM, KS and IGMV. Methodology: MM, KS, AKJ, AS and IGMV. Writing original draft: MM. Writing review and editing: MM, KS, JG, CCM, AS, SAQ, AKJ, EB and IGMV. Funding acquisition: KS and IGMV. Guarantors: MM and IGMV.

Funding This work was sponsored by the Health Programme 2014-2020 from the European Union, grant number 664609 HP-PJ-2014.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Annex 2. EuroDHYAN WP 6.1b

Ethnic differences in serum carotenoids and their association with Type 2 Diabetes within the HELIUS study

Paola Flores Sanchez[1], Mirthe Muilwijk[1], Mary Nicolaou[1], Marieke Snijder[1,2], Ron Peters[1], Irene van Valkengoed[1]

Abstract

Background: Ethnic minorities living in Europe have a prevalence of type 2 diabetes (T2D) two to five times higher than the majority population. Differences in the intake of fruit and vegetables may play a role. Serum carotenoids, a reliable biomarker of fruit and vegetable intake, have been associated with T2D. However, studies among ethnic minorities are scant.

Objective: To investigate the contribution of fruit and vegetable intake, determined by serum carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, lycopene and zeaxanthin), to differences in T2D prevalence between Dutch, South-Asian Surinamese, African Surinamese, Turkish and Moroccan origin groups.

Design: Cross-sectional data on 204 Dutch, 203 South-Asian Surinamese, 204 African Surinamese, 203 Turkish and 200 Moroccan participants from the HELIUS (Healthy Life in an Urban Setting) study were used. Age-adjusted serum carotenoid concentrations were compared using ANCOVA. Multivariate Cox regression was used to estimate prevalence ratios (PR) and their 95% confidence intervals (CI) of the association between serum carotenoid concentrations and T2D. PRs of the model adjusted for potential T2D risk factors and the model additionally adjusted for serum carotenoid concentrations were compared to study the contribution of fruit and vegetable intake to the ethnic inequalities in T2D.

Results: T2D prevalence varied from 4.9% in the Dutch population to 23.6% in the South-Asian Surinamese group. Serum carotenoid concentrations differed across ethnic groups. The highest age-adjusted serum carotenoid concentrations were found in the Dutch and Turkish populations, whereas Moroccans had the lowest concentrations of most carotenoids. After adjustment for potential confounders, the serum concentrations of total carotenoids (PR=0.67, 95% CI=0.54, 0.84), α-carotene (PR=0.57, 95% CI=0.42, 0.77), ß-carotene (PR=0.45, 95% CI=0.32, 0.63) and ß-cryptoxanthin (PR=0.73, 95% CI=0.58, 0.92) were inversely associated with prevalent T2D. These associations remained constant by sex and across ethnic groups. The differences in serum carotenoid concentrations found did not explain the ethnic inequalities in the prevalence of T2D.

Conclusions: The intake of fruit and vegetables, measured by serum carotenoid concentrations, differed significantly across ethnic groups. However, the differences in the concentrations did not explain the ethnic inequalities in T2D in our population.

Annex 3.EuroDHYAN WP 6.1d

Population distribution of handgrip strength

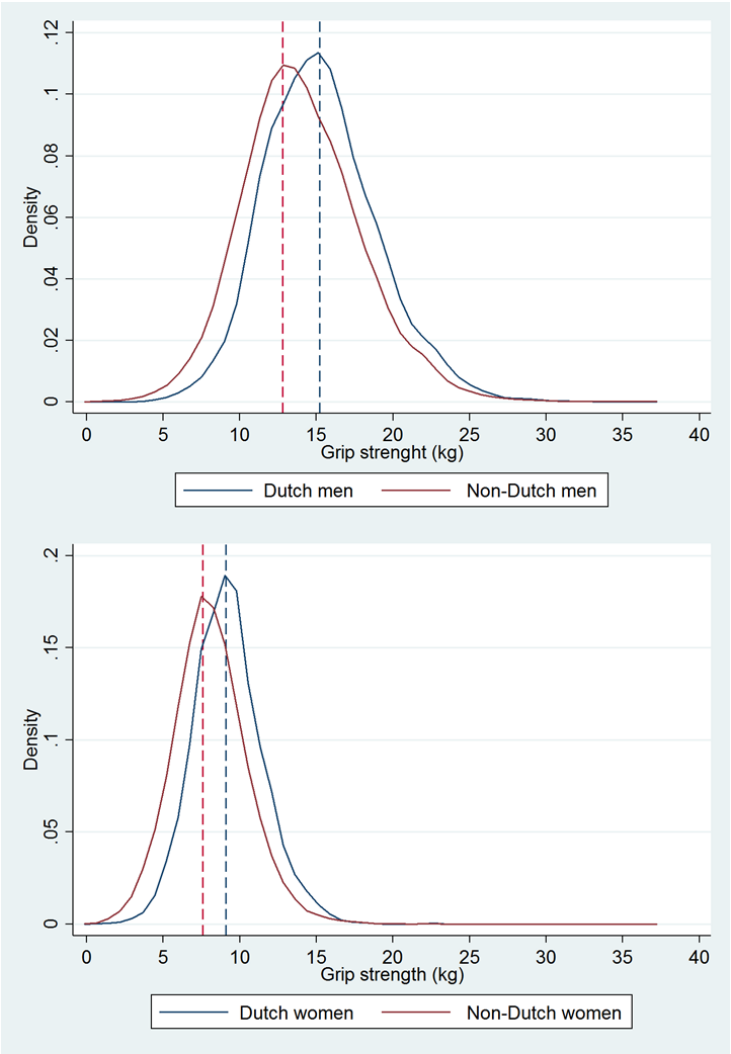

Figure 1. Distribution of grip strength expressed in absolute terms in men (upper graph) and women (bottom graph) in the HELIUS study.

Annex 4. EuroDHYAN WP 6.1a

Dietary and physical activity recommendations to prevent type 2 diabetes in South Asian adults: a systematic review

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Abstract

Intervention trials and guidelines for the prevention of type 2 diabetes (T2D) in populations of South Asian origin often include strategies to improve diet and physical activity that are based on those developed for other populations. These may be suboptimal for the South Asian target populations. We aimed to provide an overview of included recommended dietary and physical activity components, and to identify whether these were supported by evidence of their effectiveness. Databases were searched until September 2017 for intervention studies and guidelines with an adult South Asian population without T2D. The protocol was registered in PROSPERO, registration number: CRD42015207067. The quality of included studies and guidelines was assessed. Dietary and physical activity components, and effects on T2D incidence, glycemic status and adiposity measures, were summarized in tabular format and evaluated narratively. Eighteen intervention studies and four guidelines were identified. Dietary and physical activity components were similar to recommendations for the general population. Intervention studies and guidelines did not reference evidence to support the effectiveness of components included in the intervention for South Asian populations in particular. Moreover, we were unable to assess patterns of components to determine the effects of specific components. Evaluation of current and emerging components among South Asian populations and subgroups seems necessary to formulate more specific recommendations in future intervention studies and guidelines.

Annex 5. EuroDHYAN WP 6.2a

Plasma cholesteryl ester fatty acids do not mediate the association of ethnicity with type 2 diabetes: results from the HELIUS study

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[Published as DOI: 10.1002/mnfr.201700528]

Abstract

SCOPE:
Ethnic minority groups have a higher risk of type 2 diabetes (T2D) than the host population. Our aim is to identify whether plasma cholesteryl ester fatty acids (CEFA) mediate the ethnic differences in type 2 diabetes.

METHODS AND RESULTS:
We included 202 Dutch, 206 South-Asian Surinamese, 205 African Surinamese, 215 Turkish, and 213 Moroccan origin participants of the HELIUS study (Amsterdam, the Netherlands). Logistic regression is used to determine the associations between plasma CEFA and T2D. Mediation analysis is used to identify whether CEFA contributed to the association between ethnicity and T2D. We adjusted for ethnicity, age, sex, smoking, physical activity, and BMI. Associations between plasma CEFA and T2D were similar across all ethnic groups. Although differences in plasma CEFA across ethnic groups were observed, CEFA did not mediate the differences in T2D prevalence between ethnic groups.

CONCLUSION:
Although ethnic differences in plasma CEFA are found and CEFA are associated with T2D, CEFA does not contribute to the difference in T2D prevalence between ethnic groups. If confirmed, this implies that maintenance of the more beneficial CEFA profiles in the non-Dutch ethnic groups may be encouraged to prevent an even higher prevalence of T2D in these groups.

Annex 6. EuroDHYAN WP 6.2b

The association of acylcarnitines and amino acids with age in Dutch and South-Asian Surinamese living in Amsterdam, the Netherlands.

Mirthe Muilwijk[1], Frédéric M. Vaz[2], Carlos Celis-Morales[3], Ron Peters[4], Marieke B. Snijder[1], Jason M.R. Gill[3], Irene G.M. van Valkengoed[1]

Abstract

Background: Diseases such as type 2 diabetes and cardiovascular disease occur more frequently, and already at a younger age, in South-Asians than Europeans. This may be related to differences between groups in dysregulation of intermediary and fatty acid metabolism during aging. Therefore, we assessed differences in acylcarnitine and amino acid concentrations between Dutch and South-Asian Surinamese men and women, by age.

Methods: We measured types of acylcarnitine and amino acid concentrations in plasma (by tandem-MS) in a random subsample of 350 Dutch and 350 South-Asian Surinamese origin participants of the HELIUS study (Amsterdam, The Netherlands). We derived principal components (PCs) from the metabolites by principal component analysis. Linear regression was used to assess differences in PCs and individual metabolite concentrations, and their age-trends between Dutch and South-Asian Surinamese participants. We adjusted for BMI in our models, and additionally for energy intake and fat intake in sensitivity analyses.

Results: Two PCs were identified. Acylcarnitines had negative loadings on PC1, while amino acids had positive loadings on PC2. Most metabolite concentrations were higher among South-Asian Surinamese participants than Dutch participants; amino acids in women, and both acylcarnitines and amino acids in men. Metabolite levels increased similarly with age in both ethnic groups. For example, PC1 significantly decreased in both men and women. PC2 increased particularly in women; 122.4% (95%-CI: 74.4;201.2) of the baseline value for a ten years increase in age in Dutch women and 204% (95%-CI: 118.4-351.6%) in South-Asian Surinamese women. Results remained similar after adjustment for lipid or energy intake.

Conclusion: Ethnic differences in metabolite concentrations suggest that the LCFA and amino acid metabolism are more disrupted among adult South-Asian Surinamese than among Dutch from a young age. During adulthood metabolites increase at similar rates in both ethnic groups.

Annex 7. EuroDHYAN WP6.2c

Association of acylcarnitines and amino acids with incident T2D in Dutch and South Asians.

	Incident T2D
	HR (95%-CI)
Acylcarnitines	
C0	0.97 (0.74; 1.29)
C2:0	0.75 (0.58; 0.98)
C3:0	0.83 (0.63; 1.11)
C4:0	0.49 (0.36; 0.67)
C4:3OH	0.74 (0.56; 0.98)
C5:0	1.50 (1.10; 2.03)
C6:0	0.41 (0.31; 0.55)
C8:0	0.98 (0.76; 1.27)
C3DC	0.66 (0.50; 0.86)
C10:0	0.95 (0.73; 1.24)
C10:1	1.08 (0.85; 1.38)
C5:DC	0.58 (0.44; 0.77)
C12:0	0.55 (0.41; 0.73)
C12:1	0.65 (0.50; 0.83)
C6:DC	0.64 (0.49; 0.83)
C12:1OH	0.79 (0.61; 1.01)
C12OH	0.46 (0.33; 0.65)
C14:0	0.81 (0.62; 1.06)
C14:1	0.86 (0.67; 1.11)
C14:2	1.22 (0.95; 1.56)
C14:1OH	0.81 (0.62; 1.06)
C16:0	0.79 (0.60; 1.02)
C16:1	0.80 (0.62; 1.05)
C18:0	0.58 (0.44; 0.76)
C18:1	0.62 (0.48; 0.80)
C18:2	1.16 (0.89; 1.51)
Amino acids	
Leucine	2.18 (1.57; 3.03)

Isoleucine	2.89 (2.11; 3.94)
Valine	1.20 (0.89; 1.60)
Phenylalanine	1.81 (1.37; 2.40)
Tyrosine	1.26 (0.95; 1.68)
Tryptophan	1.23 (0.92; 1.65)
Alanine	2.27 (1.66; 3.10)
Methionine	1.71 (1.32; 2.22)
Glycine	0.45 (0.32; 0.61)
Glutamate	1.88 (1.40; 2.53)
Glutamine	0.39 (0.30; 0.51)
Citrulline	1.05 (0.79; 1.40)
Ornithine	0.78 (0.57; 1.06)
Lysine	1.45 (1.10; 1.91)
Arginine	1.11 (0.86; 1.45)
Serine	1.25 (1.04; 1.51)
Proline	2.76 (2.08; 3.65)
Asparagine	2.32 (1.75; 3.07)
Aspartate	1.24 (0.99; 1.55)

Prentice weighted proportional hazard cox regression of metabolites with incident T2D among Dutch and South Asian participants of the HELIUS study. Analyses were adjusted for sex, age, packyears of smoking, physical activity BMI and waist circumference. No multiplicative interaction for ethnicity was found.

Annex 8. EuroDHYAN WP6.2d

Ethnic differences in sphingolipid concentrations

	South-Asian Surinamese	
	C (nM) (95%-CI)	**p-value**
GlcCerd18:2	-49.4 (-88.9; -9.8)	***0.01***
GlcCerd18:1	-437.3 (706.6; -168.1)	***0.002***
LacCerd18:2	-50.2 (-80.0; -20.4)	***0.001***
LacCerd 18:1	-381.1 (-590.7; -171.5)	***<0.001***
CTHd18:2	13.1 (-3.7; 29.8)	0.13
CTHd18:1	1.2 (-69.2; 71.6)	0.97
Cerd18:2	12.2 (-80.4; 104.8)	0.80
Cerd16:1	-69.1 (-107.5; -30.7)	***<0.001***
Cerd17:1	-70.3 (-103.9; -36.8)	***<0.001***
Cerd18:1	-150.4 (-722.4; 421.6)	0.61
Cerd20:1	14.9 (-6.8; 36.5)	0.18
Cerd18:0	109.2 (-71.2; 289.7)	0.23
Cerm18:0	2.60 (-0.3; 5.5)	0.08

Ethnic differences in sphingolipid concentrations of South Asians compared to Dutch by multiple linear regression. P-values were given for the difference in metabolite concentration between participants of Dutch and South Asian ethnicity. P-values <0.05 were considered statistically significant and are marked in bold italic.

Annex 9. EuroDHYAN WP 6.2e

CRP mediates ethnic differences in type 2 diabetes: results from the HELIUS study

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Abstract

Scope: The prevalence of type 2 diabetes (T2D) is higher among ethnic minority populations living in the Netherlands than among the majority population. Our aim was to identify whether C-reactive protein (CRP), a marker for inflammation, mediates these differences in T2D.

Methods: We included 1000 Dutch, 999 South-Asian Surinamese, 999 African Surinamese, 1000 Ghanaian, 1000 Turkish and 1000 Moroccan origin participants of the HELIUS study (Amsterdam, the Netherlands). Differences in CRP levels were determined by multivariate linear regression. The association of CRP with T2D was determined by logistic regression, and the interaction between CRP and ethnicity was checked. Mediation analysis was used to identify whether CRP contributed to the association between ethnicity and T2D. We stratified for sex and adjusted for ethnicity (where appropriate), age, physical activity, smoking, body mass index (BMI) and waist circumference (WC).

Results: CRP levels were higher in participants of ethnic minority origin than those of Dutch origin. There was a positive association between CRP and T2D, which was similar across ethnic groups (e.g. OR 1.35 [95% CI 1.20; 1.58] for prevalent T2D among women, unadjusted for BMI and WC). The association was, however, almost fully attenuated when adjusted for measures of adiposity levels (e.g. OR 1.12 [95% CI 0.96; 1.31 for prevalent T2D among women]). CRP partly mediated the effect of ethnicity on T2D prevalence in South-Asian Surinamese men and African Surinamese, Ghanaian and Turkish women, but only in the models that were unadjusted for adiposity levels.

Conclusion: CRP may explain a small part of the ethnic differences in T2D prevalence, but other factors might be more important to reduce ethnic differences.