Personalized lifestyle interventions for the prevention and treatment of type 2 diabetes

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GENERAL DISCUSSION

It is clear from literature that lifestyle plays an important role in both the cause as well as the solution for obesity and type 2 diabetes.[1,2] However, studies investigating the effects of lifestyle in the prevention or treatment of type 2 diabetes show great heterogeneity in results.[3–8] This may be explained by large inter-individual differences in response to lifestyle interventions, as a result of differences between individuals in phenotype, genotype, current lifestyle, preferences and goals.[9] Therefore, personalized or tailored lifestyle interventions, taking into account such interindividual differences, may be more beneficial. The research described in this dissertation aims to contribute to a better understanding of the potential of personalized lifestyle interventions in the prevention and management of type 2 diabetes in achieving better health outcomes as compared to generic lifestyle advice or care as usual. To this end, two personalized lifestyle intervention studies were performed in a preventive setting (**Chapters 2 and 3**), two personalized lifestyle treatment studies were performed in a primary care setting (**Chapters 4 and 5**) and two explorative studies were performed to investigate if continuously measured glucose and contextual data can be used for personalization of lifestyle advice (**Chapters 6 and 7**). Lastly, a viewpoint paper was written describing design issues in developing a personalized nutrition advice system (**Chapter 8**).

Summary of main findings

The first aim in this dissertation was to investigate if a personalized lifestyle approach is more effective as compared to generic dietary advice in optimizing health status, in the prevention of lifestyle-related diseases. In both preventive real-world studies, personalized lifestyle advice resulted in an improved adherence to dietary guidelines after the intervention. Additionally, subtle objective changes in health status were observed. In **Chapter 2** healthy free-living seniors participated in a 9-week personalized advice and behavior change intervention, in which personalized advice was based on metabolic health measurements, genetic variants (SNPs) and current dietary intake, and resulted in a set of nine personalized recommendations ordered for which behavior change was most urgent, seven of which focused on diet and two on physical activity. After the intervention, improvements were seen in adherence to the dietary guidelines for saturated fat, omega-3 fatty acids, liquid, and salt. Also, there were subtle additive beneficial health effects, with a larger decline in body fat percentage, waist circumference and hip circumference, among those receiving personalized advice as compared to those only receiving generic advice. In **Chapter 3** healthy male and female employees participated in a 10-week personalized systems nutrition program in an at-work setting. At the start of the intervention, phenotypic, genotypic, and behavioral data were fed into algorithms that grouped participants into seven diet types guiding macronutrient recommendations, and to generate personalized caloric intake and micronutrient recommendations. Finally, participants were provided with personalized recipes and meals according to their macro- and micronutrient recommendations. The intervention led to a reduced intake of total and saturated fat, sugar, and sodium. Additionally, there was a significant reduction in BMI, body fat and hip circumference. In both studies personalized advice based on biological data, including anthropometrics, blood pressure, clinical chemistry, and phenotypic flexibility (glucose and lipid response to a mixed meal challenge test) was combined with behavioral change support, consisting of feedback on health status, formulating implementation intentions or setting personal goals and/or motivational interviewing. Interestingly, in both studies effects were found on anthropometrics, while the intervention did not include caloric restriction nor focused on weight loss. Although in both studies a holistic approach towards personalized lifestyle was applied, effects on health status were modest.

The second aim in this dissertation was to investigate if a personalized lifestyle approach based on type 2 diabetes pathophysiology (diabetype) is more effective in ameliorating this disease as compared to care as usual. Amelioration of type 2 diabetes was operationalized as achieving type 2 diabetes remission, i.e. normalized HbA1c (< 48 mmol/mol) and fasting glucose (≤6.9 mmol/L) without the use of glucose-lowering medication, or achieving type 2 diabetes reversal, i.e. attaining target values for HbA1c (≤53 mmol/mol) and fasting glucose (<8.0 mmol/L) with reduced medication, or attaining normalized HbA1c (< 48 mmol/mol) and fasting glucose (≤6.9 mmol/L) with equal medication. Additionally, we aimed to investigate the feasibility of implementing a personalized lifestyle approach for people with type 2 diabetes in primary healthcare. In **Chapters 4 and 5** we show that personalized lifestyle interventions can result in remission or reversal of type 2 diabetes, even for people with longer type 2 diabetes duration. Results from these studies indicate that tailored treatment based on the underlying pathophysiology of type 2 diabetes may have added value over a one-size fits all approach, as fasting plasma glucose and Hepatic Insulin Resistance Index (HIRI) specifically improved in the groups with (isolated) liver insulin resistance, and postprandial glucose decreased in subgroups with muscle insulin resistance. In **Chapter 4** the weight loss is sustained, i.e., also 2 years after the intervention a significant reduction in body weight and HbA1c was still present. In groups with liver insulin resistance, this was addressed via a (very) low caloric diet, whilst postprandial glucose excursions and muscle insulin resistance were targeted via a tailored strength and endurance training intervention. Although HbA1c and fasting glucose improve or even normalize in these studies, underlying pathophysiology is minimally affected, especially for groups with isolated impaired beta cell function or a complex phenotype with combined muscle and hepatic insulin resistance. This advocates that even when remission is achieved, continued monitoring and long-term adherence to (tailored) lifestyle treatment is required.

The third aim in this thesis was to explore the usability of continuous glucose monitoring for personalized lifestyle advice for the prevention and treatment of type 2 diabetes. Additionally, we aimed to investigate if lifestyle interventions result in differential effects on acute glucose metabolism, and if this can be related to underlying type 2 diabetes pathophysiology (diabetype). In **Chapter 6** the potential of real-life personalized nutrition approaches using Continuous Glucose Monitoring (CGM), activity tracking, sleep monitoring, and food diaries was explored in a real-world setting. Our results show that physical activity, dietary intake, and sleep have a significant impact on glucose values, with physical activity and nutrition being equally important for the prediction of the glucose peak, whereas sleep has a lower contribution to this prediction. Additionally, cardiometabolic features and individual-specific factors affected glucose levels, indicating substantial interindividual variability in glucose responses. Using the Shapley additive explanation (SHAP) approach, we show there is indeed large interindividual variation in the importance of lifestyle factors in predicting glucose peaks. This is a first, significant step toward providing personalized, real-time lifestyle recommendations based on self-monitoring data. After further validation, such models could facilitate self-management by offering personalized lifestyle recommendations for maintaining a healthy glucose metabolism. In **Chapter 7** we show that lifestyle interventions result in beneficial effects on metrics of continuous glucose monitoring (CGM) within four days. However, the impact of lifestyle interventions on CGM metrics was largely dependent on carbohydrate intake at baseline. Our data suggest that the type of tissue affected by insulin resistance (i.e., liver and/or muscle) as well as the remaining beta-cell capacity are determinants of the direction and size of the effects of distinct lifestyle interventions. Therefore, determining the disease phenotype of an individual may allow for personalized lifestyle advice and treatment of type 2 diabetes mellitus.

Holistic approach for personalized lifestyle

In **Chapters 2, 3 and 5** we applied a holistic approach for personalized lifestyle advice. These are among the first studies in which such a comprehensive approach for personalized lifestyle is used, in which personalized recommendations are based on a combination of data related to phenotype, lifestyle, personality and genotype (chapters 2 and 3 only) and is being combined with (personalized) behavior change support such as goal setting. For the SNPs that were included evidence exists that the interaction between the risk variant of the SNP and health status can be influenced by lifestyle. Other studies in the field of personalized lifestyle so far have mainly focused on providing personalized dietary recommendation based on either phenotypic or genotypic data, in some cases combined with data on current dietary intake.[10] Few studies have investigated the effects of a more comprehensive personalized lifestyle advice combining several sources of data, including phenotype, genotype and/or lifestyle behavior.[11,12] Also, only few studies, including ours, incorporated behavior change theory or techniques in their intervention, whilst it is known that merely providing information is often not sufficient to motivate people to change their behavior. Lifestyle interventions should be underpinned with behavior change theory to increase the effectiveness of lifestyle interventions.[13,14]

Effect of personalized lifestyle advice on dietary intake

In **Chapters 2 and 3** we demonstrate that a holistic approach for personalized lifestyle advice can lead to beneficial changes in lifestyle behavior. Dietary intake improved for some, but not all nutrients in the personalized advice group. In both studies, as well as in the Food4Me study, the intake of (saturated) fat and salt improved.[11] Dietary intake improved particularly in people in whom the intake at baseline was suboptimal. If personalized nutrition is indeed more effective in improving dietary intake for food groups or nutrients for which intake is suboptimal, this could be a good strategy to pursue, besides the current public health efforts focused at improving adherence to national dietary guidelines. Despite an overall improvement in dietary quality in the Netherlands over the last decade, a significant proportion of the population still does not adhere to the national dietary guidelines. Personalized nutrition could help by giving advice relevant to the individual, which might make people more motivated to change their diet. A recent meta-analysis of 11 randomized controlled trials (RCTs), concluded that personalized dietary advice was better at improving dietary intake in healthy adults than generic nutritional advice, although results varied largely between studies[10]. It should be noted that personalized dietary advice can be based on multiple factors, including the more subjective personal preferences on the one hand and objective physiology-based markers on the other hand, and combinations of those. Given the large heterogeneity in studies so far, from the meta-analysis no definitive conclusions can be drawn on what are the most effective (combinations of) bases for personalization. In our studies dietary intake did not change for all nutrients, such as protein, that had room for improvement at baseline. This suggests that personalized dietary advice may not lead to a perfectly healthy diet, or that further improvement of the personalized dietary advice system and behavior change support are required. Another personalized nutrition study, investigating the effects of personalized advice on the intake of food groups, suggested that nutritional behavior improved to a larger extend for food groups for which personal goals were set.[12] More research is required to identify the key determinants of success of personalized lifestyle interventions in changing dietary intake. However, effects of personalized dietary advice on dietary intake only provide one part of the puzzle, it is also of interest to investigate the effects of personalized advice on health status.

Effect of personalized lifestyle advice on health status

In **Chapters 2 and 3** we show that personalized lifestyle advice can lead to beneficial changes in health status. Both studies, although not focusing on reducing caloric intake, resulted in weight loss and improvements in body composition. Although beneficial health effects were modest, with weight loss of less than 5%, these may still be meaningful as these studies lasted 9 respectively 10 weeks, which may be too short for changes in some clinical biomarkers to occur. The traditional clinical biomarkers included in these studies are also not necessarily suitable for picking up the mostly subtle effects of nutrition on health, and, given the personalized nature of the intervention, the main outcome of interest differed between individuals. The inclusion of additional biomarkers or metabolites that better reflect metabolic processes could provide more direct insight in the effects of personalized nutrition strategies. Another explanation for the relatively small health effects in our studies is that participants were encouraged to set small and realistic behavior change goals, which are easier to sustain in the long run than more drastic changes in behavior which may have a more immediate but potentially only short-term effect on health. In **Chapter 3**, personalized advice was most effective in the subgroup with the most compromised health status. This suggests personalized advice may be more beneficial for subgroups with more room for health improvement. This was shown before in overweight persons subjected to weight loss. Only persons who were metabolically compromised at baseline improved in terms of metabolic health, whereas persons that were metabolically healthy did not show improved metabolic health although significant weight loss.[15] It could be that subgroups who were unaware of their health status and are confronted with their suboptimal health data may be more motivated to change their lifestyle as compared to subgroups confronted with more optimal health data. It could be that individuals with a higher compromised health status are more motivated to change their lifestyle as compared to healthy individuals, as it has been previously suggested that motivation is key in adopting a healthy lifestyle.[16] Also, research showed that individuals who were aware of their compromised metabolic health had a more favorable attitude towards personalized nutrition.[17] However, another study showed that a higher perceived risk of developing diabetes does not necessarily lead to a greater intention to adopt healthier lifestyles.[18] There are some suggestions that personalized advice based on genotypic data is not more effective than personalized advice based on behavioral or phenotypic data.[10,19] However, effectivity of personalized advice is not only dependent on effects of personalized advice on behavior change, but is also determined by the effectivity of personalized advice in influencing an individual's biology. In general, it is unclear which types of measurements or combinations thereof are most important to include into personalized lifestyle advice systems.

Personalization based on the diabetype

In **Chapters 4 and 5** personalized lifestyle treatment was (partly) based on the diabetype of an individual, i.e., the type of tissue affected by insulin resistance (i.e., liver and/or muscle) as well as the remaining beta-cell capacity. We hypothesized that this diabetype would determine the response to a lifestyle intervention, due to metabolic differences between these diabetypes. Results from these studies indicated that tailored treatment based on the underlying pathophysiology of type 2 diabetes may have added value over a one-size fits all approach, as fasting plasma glucose and Hepatic Insulin Resistance Index (HIRI) specifically improved in the groups with (isolated) liver insulin resistance, whereas postprandial glucose decreased in subgroups with muscle insulin resistance. In groups with liver insulin resistance, this was addressed via a (very) low caloric diet, whilst postprandial glucose excursions and muscle insulin resistance were targeted via a tailored strength and endurance training intervention. A recent study investigating effects of personalized dietary advice based on their metabolic phenotype, showed that a diet high in protein and fiber resulted in greater benefit in individuals with predominantly muscle insulin resistance, whilst a diet high in MUFA resulted in greater health benefits in people with predominantly liver insulin resistance.[20] This suggests that certain lifestyle strategies or combinations thereof may be effective for specific metabolic phenotypes or diabetypes. This is also apparent from our study investigating the differential effects of lifestyle interventions on CGM metrics between diabetypes. The low carbohydrate diet was for instance more effective in lowering mean glucose levels and glucose variability in people with hepatic or combined insulin resistance as well as impaired beta-cell function as compared to people with isolated poor beta-cell function. For this latter group, it seems that a combination of a low carbohydrate diet with a physical activity intervention is most effective in improving CGM metrics.

It should be noted that the diabetype is only one part of the puzzle, factors like body composition, microbiome composition, inflammatory profile and overall cardio-metabolic health may also influence intervention effectiveness. Besides, in providing personalized lifestyle advice, current lifestyle, personal preferences, and the socio-economic environment are preferably also considered.

Personalized lifestyle behavior change support

In **Chapters 2 and 3** personalized advice based on biological data was combined with behavioral change support, consisting of for instance feedback on health status, formulating implementation intentions, setting personal goals and/or motivational interviewing. Even though in our studies a holistic approach including behavior change support towards personalized lifestyle was applied, effects on health status were modest. This could partly be explained by the short duration of these studies, as well as the focus in these studies on setting small but realistic behavior change goals. Although small goals may result in more modest changes in lifestyle behavior and health, this was a deliberate choice, as it has been shown that a large discrepancy between the current state and the personal goal can result in low self-efficacy and negative outcome expectancies.[21] Especially self-efficacy is a strong determinant of lifestyle behavior. Small, but realistic goals may be easier to achieve and to maintain on the long term. Previous meta-analyses have shown goal setting or action planning are indeed among the most effective behavior change techniques in promoting change in healthy eating and physical activity.[22,23] Other effective strategies include instruction on how to perform a behavior, receiving feedback on behavior or outcomes and motivational interviewing.

Whilst lifestyle advice was personalized in our studies, the included behavior change techniques were equal for all participants. It is however likely that individuals differ in the type of behavior change support that works best for them, especially considering differences in personality, motivation and the multi-factorial nature of eating behavior and eating environment.[24] Additionally, in our studies we only included four to eight behavior change techniques, while the most effective studies in terms of weight loss in a meta-analysis included 7 to 14 different behavior change techniques, suggesting that combining multiple behavior change techniques increases intervention effectiveness.[25] In this same meta-analysis, however, no differences in terms of weight loss were found between personalized feedback and control interventions that lasted up to 12 months, highlighting the need for identifying and integrating behavior change techniques and support tools for long-term behavior change. A qualitative study suggests that personalization, self-monitoring, praise and suggestions may be effective persuasive system design principles for long-term behavior change support.[26] Therefore, to increase the effectivity of personalized lifestyle advice systems possibly the focus should not only be on inter- and intraindividual differences in the physiological or biological response to food and nutrients, but on integrating continuous (self-)monitoring of and feedback on health status, behavior and real-life environments to optimize personalized advice.[27] This requires the shift from generic or targeted behavior change interventions to adaptive interventions, such as just-in-time adaptive interventions (JITAIs) that are adapted based on individual's responses to the intervention using prespecified algorithms[28], or even continuous-tuning interventions, i.e. interventions that are adjusted and adapted to the changing needs of an individual based on their own data and real-time algorithm optimization.[29]

Strategies to personalize lifestyle advice for the prevention and treatment of type 2 diabetes

As described, there are many possible strategies to lifestyle advice for the prevention and treatment of type 2 diabetes, including extensive phenotyping, considering personal preferences, using behavioural change techniques, continuous monitoring and using genetic risk profiles. Which strategies are most fitting, is dependent on the goal of the personalized lifestyle advice system as well as on the target group. More extensive phenotyping, including diabetyping, may be more relevant in already metabolically compromised individuals and less relevant in healthy individuals. Especially since in healthy individuals it is more difficult to achieve metabolic health improvement. However, there seems to be a limited window of opportunity to intervene with lifestyle in reversing or halting progression of type 2 diabetes, as in people with severe type 2 diabetes, and especially in those with poor beta-cell functioning, lifestyle interventions have limited health effects. This underlines the importance of early detection of (pre)diabetes type 2 and other lifestyle-related diseases, but also stresses the importance of the integration of lifestyle treatment in the healthcare system. A more personalized approach could help increase the effectiveness of lifestyle treatment in healthcare. People with type 2 diabetes should for instance be encouraged by their caregiver to set realistic personal goals on lifestyle change and be equipped with the proper tools or skills to achieve and maintain this lifestyle change. Personalized advice systems integrated in the healthcare system could play a role in this goal setting, behaviour change support and progress monitoring. Which type of goal setting, behaviour change guidance and progress monitoring is used, should be tailored to the individual or patient considering their skills and preferences. Integrating continuous monitoring using wearables and digital tools in health care could provide an interesting opportunity to allow individuals to self-manage their disease and educate themselves on the influence of lifestyle on their health status. However, as promising new wearables, sensors and tools may be, these are, in their current form, especially beneficial for the digitally and (health) literate individuals. Digital and/or health illiterate individuals may currently benefit more from going to a health care professional for follow-up measurements and lifestyle recommendations, or from being part of a peer group for e.g., lifestyle education, cooking lessons, physical activity classes and support.

CONCLUSION

In this thesis we aimed to further substantiate the potential of personalized lifestyle interventions in the prevention and management of lifestyle-related diseases, with a focus on type 2 diabetes, in achieving better health outcomes as compared to generic lifestyle advice or care as usual.

The research described in this thesis shows that personalized lifestyle interventions may lead to beneficial changes in lifestyle behaviour and health status. In a healthy population these changes are especially apparent if there is more room for improvement, suggesting personalized lifestyle may be more effective for health-compromised subgroups. However, additive beneficial effects of personalized lifestyle were modest, even though a holistic approach was taken in which personalization was based on an integrated data set containing phenotypic, genotypic, and behavioural data, and behaviour change techniques were applied. In the populations with type 2 diabetes, larger beneficial health effects were seen after the intervention, suggesting personalized lifestyle advice may indeed sort larger health effects in more health compromised populations. Given these large differences in health effects between populations, the added value of integrative personalized lifestyle approaches, should be carefully weighed against the burden and cost of data collection. In more healthy populations, personalized lifestyle approaches could for instance predominantly use less burdensome measurements and tools, for instance using mainly do-it-yourself techniques and wearables. In more health compromised populations, on the other hand, more burdensome measurements, such as challenge tests, may be better justified and even necessary. This added value could potentially be increased by providing individuals with real-time personalized advice, considering their current context. Not only because this allows providing personalized advice at the right time, but also because our data show that there are large interindividual differences in the glucose response to lifestyle, and that these glucose responses can be predicted using contextual data. In people with type 2 diabetes, the differences in both the direct and more intermediate response to lifestyle interventions could partly be explained by the underlying pathophysiology of an individual, the diabetype. This suggests that more detailed characterization of the disease phenotype may be of importance for optimal lifestyle advice and guidance and personalized treatment of type 2 diabetes mellitus.

Future perspective

Also, unraveling whether beneficial health effects of personalized interventions are due to increased adherence because of tailoring recommendations towards an individual's biology, due to personalized behavior change support, or due to the combination of both, requires dedicated trials. Since the added value of personalized lifestyle advice may be twofold, increasing health effects of an intervention, as well as in promoting adherence to a healthier lifestyle, at the very least both should be included as outcome measurements in personalized lifestyle studies.

An important question is what appropriate study designs are for investigating effects of personalized lifestyle approaches. Traditionally, randomized controlled trials are considered the golden standard for investigating food-health relations. However, these result in population averages and may not fully capture interindividual differences. Randomized controlled trials may be suitable to investigate the concept of personalized advice, by studying group level effects on health or behavior of personalized advice as compared to more generic recommendations. However, to investigate the effects of personalized advice for individuals, study designs focusing on individual responses, such as n-of-1 studies, modelling or segmented analyses may be more suitable. Also, multi-arm or hierarchical designs could be considered to assess which components of a personalized lifestyle approach have added value, and which components could be omitted. Gaining more insight in the most effective components of personalized lifestyle could also benefit the scalability and cost-effectiveness of personalized lifestyle approaches.

In research on personalized lifestyle advice not only its effects on health or behavior should be considered, but also the clinical relevance and added value thereof in relation to the burden of frequent or invasive measurements for individuals. In this respect, it should be considered how unique or different personalized recommendations are as compared to the general dietary guidelines, and if full personalization is necessary or if for instance identifying comparable subgroups could suffice. In this thesis we for instance showed that diabetypes based on tissue-specific IR and beta-cell functioning may be a valuable target for more tailored lifestyle treatment for people with type 2 diabetes. These diabetypes however only capture part of the picture. Research investigating the interaction between diet and (postprandial response of) other metabolites, including for instance lipids, short-chain fatty acids and inflammatory markers, could provide direction for further phenotyping and personalization. Moreover, our studies on continuous monitoring demonstrated the potential of more real-time advice. Research on integrated personalized advice tools, combining real-time monitoring of lifestyle and glycemic response and just-in-time personalized recommendations should demonstrate the feasibility and effectiveness of such tools in a real-life setting in treatment, but also prevention of type 2 diabetes.

As in the studies in this thesis the personalized advice interventions were all relatively short-term, no definitive conclusions can be drawn from this research on the sustainability of lifestyle changes because of personalized lifestyle advice. Future studies should investigate the longer-term effects of personalized lifestyle approaches on health and lifestyle behavior in daily life as well as its effects on and feasibility in healthcare.

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