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

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1

GENERAL INTRODUCTION

Role of lifestyle in prevention and management of non-communicable diseases

Non-communicable diseases, including cardiovascular disease, diabetes and cancer, accounted for over 40 million deaths and more than 70% of total mortality worldwide in 2017.[1] Over 80% of the aforementioned fatalities were deemed avoidable premature deaths, that is deaths that could have been prevented through the implementation of efficacious public health protocols, lifestyle interventions or amenable to good quality health care.[2] Indeed, diet-related risk factors are held responsible for about one quarter of all deaths among adults.[3] Shifting from being inactive to meeting the recommended level of 150 minutes of moderate-intensity aerobic physical activity has been associated with a 23% reduced risk of cardiovascular mortality.[4] The major non-communicable diseases share four behavioural risk factors, including unhealthy diet, physical inactivity, alcohol abuse and smoking.[5] These risks factors play a role in both the prevention and management of non-communicable diseases. Adopting a healthy lifestyle can for instance largely reduce the risk of type 2 diabetes[6], but is also associated with a substantially lower risk of cardiovascular disease and all-cause mortality for people with type 2 diabetes.[7] For nearly all adults, however, consumption of healthy foods and nutrients is suboptimal,[3] and one out of four adults does not meet the global recommendations for physical activity as set by WHO.[8,9]

Lifestyle interventions for the prevention or treatment of type 2 diabetes

The question rises what comprises a healthy lifestyle for prevention or treatment of type 2 diabetes. It is clear that both diet and physical activity play an important role in both the cause as well as the solution for obesity and related diseases.[6,10] Two large programs, the Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP), both resulted in a 58% reduction in the incidence of diabetes.[11–13] The DPP prescribed a minimum of 7% weight loss, by focusing on calorie reduction and reducing fat intake, and 150 minutes of moderate intensity aerobic exercise per week. In the DPS the prescribed weight loss was similar, with a minimum of 5%. However, dietary recommendations focusing on increasing fibre intake, reducing saturated fat, and increasing monounsaturated fat as well as physical activity recommendations, consisting of a daily 30 minutes of combined aerobic and resistance training differed as compared to the DPP. When looking into specific food groups, higher intake of whole grains and cereal fibre, and moderate alcohol intake were inversely associated with type 2 diabetes incidence, whereas higher intake of sugar sweetened beverages and red and processed meat were associated with an increased type 2 diabetes incidence.[14] In individuals with type 2 diabetes all-cause mortality is inversely associated with a higher intake of fish, whole grain, fibre and n-3 polyunsaturated fatty acids.[15] At the level of dietary patterns, meta-analyses showed that several healthy diets are effective in reducing risk of type 2 diabetes, including Mediterranean diet, Dietary Approaches to Stop Hypertension or “DASH” diet, and diets compliant with the Alternative Healthy Eating Index.[16,17] For people with type 2 diabetes low-carbohydrate, moderate-carbohydrate, low glycaemic index, Mediterranean, high-protein, vegetarian, Palaeolithic and low fat diets all

significantly reduce HbA1c and fasting glucose as compared to a control diet.[18,19] In general, it seems that energy restriction and resulting weight loss play a crucial role in the positive health effects of these diets. In terms of physical activity a shift from being sedentary to meeting the physical activity guidelines of 150 minutes of aerobic exercise per week was associated with a 26% lower incidence of type 2 diabetes.[4] However, several types of physical activity may be more or less beneficial, including low, moderate and vigorous intensity activity, resistance exercise, occupational activity and walking.[20,21] Meta-analyses show that all forms of physical activity can significantly improve glycaemic control in people with type 2 diabetes, including aerobic exercise, resistance training and a combination of both.[22,23]

Inter-individual variation in response to lifestyle interventions

Even though multiple diets and types of physical activity have beneficial effects in the prevention and treatment of type 2 diabetes, studies show great heterogeneity in response to lifestyle interventions.[24–29] Although the quality of diabetes lifestyle interventions (e.g. use of established behaviour change techniques, level of patient-centricity, and intervention intensity) plays an important role in their effectiveness, especially in real-world settings,[30] evidence is emerging that inter-individual differences may affect response to lifestyle interventions. This inter-individual variation includes differences in lifestyle, preferences and goals, but also phenotypic and genotypic characteristics.[31] Given this inter-individual variation a "one-size-fits-all" dietary or physical activity plan may therefore not be the most optimal strategy in the prevention or treatment of type 2 diabetes. Indeed, consensus reports state that lifestyle interventions should be individualized for adults with prediabetes or diabetes.[32,33] Also, selected outcome or target markers may influence study outcomes. Literature has shown that some diets are more effective in reducing high glucose excursions or glucose variability, whilst other diets are more effective in influencing fasting glucose levels.[34] Therefore, studies using fasting glucose or HbA1c as main outcome may result in different conclusions as compared to studies with glucose variability as the main outcome. Which of these outcome markers is more relevant to study may depend on the target group. Individuals with prediabetes may for instance mainly suffer from impaired glucose tolerance or impaired fasting glucose or both.[35]

Pathophysiological differences between people with type 2 diabetes

Type 2 diabetes is increasingly being recognized as a heterogeneous disease, with large variation in glucose homeostasis, level of insulin resistance, disease progression and risk of complications.[36] The development of type 2 diabetes can start with isolated impaired glucose tolerance, isolated impaired fasting glucose, or a combination thereof, or with a primary defect in insulin secretion pathways.[35,37] Large heterogeneity also exists in the level of insulin secretion and insulin sensitivity,[38] which can be described as a continuum ranging from solely beta-cell failure to solely insulin resistance as the principal pathophysiological defect.[39] On top of this, insulin resistance can manifest in multiple organs, including liver, muscle and

adipose tissue.[40] Although insulin resistance commonly arises concurrently among various tissues, recent research indicates the rate, order and severity of the development of insulin resistance across these tissues may differ between individuals.[41,42] This suggests that some individuals may predominantly exhibit insulin resistance in skeletal muscle whilst in others insulin resistance may manifest primarily in the liver. Insulin resistance in skeletal muscle has been associated with impaired glucose tolerance and results in reduced glucose uptake and handling, caused by decreased GLUT4 translocation.[43,44] Liver insulin resistance has been associated with impaired fasting glucose, and leads to increased glucose production and reduced insulin suppression, contributing to higher plasma glucose concentrations. Adipose tissue insulin resistance leads to hyperglycemia through reduced glucose uptake and inhibition of lipolysis by insulin, resulting in elevated free fatty acid levels in the blood. Given this inter-individual variation, tailored lifestyle interventions for the prevention and treatment of type 2 diabetes may be more effective. For this purpose, we propose a subtyping method that determines the underlying pathophysiology for an individual with type 2 diabetes (diabetype) based on the level of muscle insulin resistance, liver insulin resistance and beta-cell function.[45] In this thesis, tailoring lifestyle interventions to subgroups or individuals will be referred to as personalized lifestyle.

Personalized lifestyle advice

Personalized lifestyle is rooted in the concept that one size does not fit all, recognizing interindividual differences in phenotype, genotype, behaviour and socio-psychological factors.[46,47] In this thesis personalized lifestyle will be limited to nutrition and physical activity, although it is being recognized that other lifestyle factors such as sleep and stress management may be equally important. So far, most studies in the field of personalized lifestyle focused on personalized nutrition. Personalized nutrition has been defined as "the use of individual-specific information, founded in evidence-based science, to promote dietary behaviour change that may result in measurable health benefits"[48] and as "a field that leverages human individuality to drive nutrition strategies that prevent, manage, and treat disease and optimize health".[49] These definitions show great overlap and are also applicable to personalized lifestyle in a broader sense. In general, there are two approaches for personalization, namely personalization based on biological evidence of interindividual differences in response to lifestyle depending on phenotypic or genotypic characteristics or personalization based on current lifestyle behaviour combined with personalized strategies for supporting behaviour change.[50] For the level of personalization, broadly, a distinction can be made between personalization based on subgroups with similar characteristics, and personalization for a specific individual. Subgroups could for instance be formed using phenotyping characteristics, such as the diabetes subtypes described by Ahlqvist et al.[36], but can also be formed using retrospective cluster analysis such as the mathematical model as proposed by Erdós et al.[51]

Strategies to personalize lifestyle advice

Even though several definitions of personalized nutrition have been given, personalized nutrition or personalized lifestyle is still a very broad concept and multiple strategies can be used for developing personalized lifestyle interventions. In fact, several strategies for personalized lifestyle have been described in literature. Three aspects always need consideration in defining the personalized lifestyle strategy that is 1) sense, or the measurements to generate personalized data; 2) reason, or how to connect the generated personalized data to nutritional advice and 3) act, or in what form the personalized advice is delivered to the individual so this individual can act on the personalized lifestyle advice. 1) In terms of data collection and input variables, personalized nutrition or lifestyle approaches can use a single measurement for personalization, but may also use complex multi-omics approaches.[52] Additionally, the types of measurements that can be included is very diverse, ranging from questionnaires (e.g. on behaviour, personality) to continuously measured sensor data. 2) For translating individual data to personalized lifestyle advice, broadly two approaches can be distinguished, namely data driven approaches and knowledge or expert-driven approaches. Data-driven approaches, such as used in the study by Zeevi et al.[53], involve using artificial intelligence or machine learning techniques, and allow for analysis of large and complex datasets. However, such models may have low interpretability due to the complexity of underlying algorithms or use of black box algorithms, and are at risk of bias as a result of inadequate sample sizes, failure to deal with overfitting or poor handling of missing data.[54] Knowledge-driven approaches, such as in the Food4Me study,[55] may involve decision trees or systems dynamics modelling based on current literature or expert knowledge. Such approaches have the advantage of having a high interpretability as the used models are often relatively simple and/or result in interpretable coefficients. However, knowledge driven decision trees such as used in the Food4Me study were generated manually, which requires a lot of time and effort, especially since underlying food-health relations are based on expert knowledge and extensive literature mining. A hybrid approach combining both can be used to provide personalized advice based on current scientific evidence, but meanwhile also using collected data to generate new nutrition-health relations. 3) Outputs of personalized lifestyle approaches can also be very diverse, ranging from textual advice to products or services. Textual advice could for instance be used in dietary recommendation systems providing individualized recommendations for intake of specific food groups, foods or specific nutrients.[56] Personalized products could consist of personalized recipes, supplements, meal boxes or even tailor-made 3D-printed foods, with personalized nutrient composition.[57] Additionally, personalized interventions may consist solely of lifestyle recommendations, products or services, or may also include personalized behaviour change support. Personalized behaviour change support could consist of taking into account personal preferences in formulating the advice, using tailored behavioural change techniques to motivate or support an individual in following the advice, or a live coach helping the individual in implementing the personalized lifestyle advice.[58] Few studies

have shown that personalized programs including support by trained professionals were more successful than programs that relied completely on self-management.[49]

Science of personalized lifestyle

For personalized lifestyle approaches, two levels of scientific substantiation could be considered. Firstly, knowledge-based personalized nutrition approaches, such as the decisions trees used in the Food4Me study, should make use of well-established and well-documented food-health relations.[59] Generally accepted principles of scientific substantiation should be at the basis of such personalized advice systems, like suggested in the genotype-based dietary advice framework by Grimaldi et al.[60] When using data-driven approaches, underlying models should be based on large, representative datasets that preferably also include data on longer term health effects.[31] Additionally, machine learning or artificial models should preferably be based on evidence-based physiological or psychosocial principles, to lower the risk of bias or confounding. However, unguided machine learning techniques can also be used in unraveling novel mechanisms, but then it is important that explainable artificial intelligence (AI) technologies are being used, so identified novel mechanisms can be scientifically validated. Secondly, the effects of the resulting personalized lifestyle intervention in improving lifestyle behavior and/or health should be assessed via dedicated trials. The required level of evidence may vary depending on potential benefits and risks of the approach.[48] Novel data-driven methods may require more rigor validation than a personalized advice system focusing on dietary preferences. Traditional methods for studying food-health relations, such as randomized controlled trials and population averages, may not be suitable for personalized nutrition as these do not capture interindividual variation.[61] Studies on personalized nutrition approaches should focus on individual or subgroup responses. This could be done using n-of-1 studies, investigating responses to multiple lifestyle interventions over time within an individual, and/or segmented analyses.[62] A recent systematic review of RCTs in the field of personalized nutrition shows that personalized approaches yield small but significantly greater improvements in dietary intake as compared to generic dietary advice.[63] However, most of the included studies focused on personalized advice solely based on phenotypic or genotypic characteristics, and only few studies also included behaviour change techniques. It is to be expected that a more holistic approach combining personalized advice based on health data with personalized strategies for behaviour change could lead to greater improvement in dietary intake or health.

Holistic approach towards personalized lifestyle

In personalized lifestyle approaches a wide range of markers can be included, such as an individual's phenotype, genotype, metabolome, and microbiome. All these markers can influence the impact of lifestyle interventions on an individual's health status or goals, but may also influence each other.[61] To develop the best fitting lifestyle interventions for individuals or specific subgroups, an understanding of the interaction between relevant

biological mechanisms is required. In other words, developing optimal lifestyle interventions for an individual may require a systems biology approach. As biological systems are not static and subject to environmental challenges, it has been proposed that health should be defined as the ability to cope with daily challenges.[64] Consumption of food or physical activity can also be seen as challenges to the system, as this requires the activation of several physiological processes, such as the production of insulin to ensure glucose levels in blood return to homeostatic levels. This ability to maintain homeostasis under changing conditions is referred to as phenotypic flexibility.[61] Measuring the phenotypic flexibility of an individual may allow for early detection of disease. For instance, in people at risk of developing type 2 diabetes, the phenotypic flexibility to adequately deal with glucose may already be reduced well before diagnosis.[65] Measuring phenotypic flexibility can be done using a challenge test, such as a mixed-meal challenge test, or an oral glucose tolerance test.[66] On top of biological mechanisms, an individual's socio-economic environment, behavior and personality also influence the interaction between lifestyle and health, and should be considered.[65] Therefore, a more holistic view on health may be required, such as proposed in the 360 diagnosis tool, where objective health measurements are combined with environmental, mental, and behavioral factors to provide a more comprehensive view of an individual's health status. [67] Lastly, in personalized lifestyle it is also important to consider which health-related goals are relevant to an individual and how an individual can be supported in achieving these goals. Personal goals may include glycemic control, optimizing endurance or strength, weight management, etc.[61] In this respect, Patient-Reported Outcome Measures (PROMs), could also be considered, such as reducing pain or anxiety and being able to perform activities of daily living, as these PROMs are the outcome measurements that matter most to patients, such as people with type 2 diabetes.[68] Several studies have shown that behaviour change support techniques can be employed to effectively achieve changes in lifestyle behaviour.[69] In personalized lifestyle interventions the use of personalized feedback may be obvious and has been shown to be effective.[70] Another meta-analysis which aimed to identify effective behaviour change techniques targeting changes in diet and physical activity in people with type 2 diabetes showed that instruction on how to perform a behaviour, practicing and demonstration of the desired behaviour and action planning were most effective in reducing HbA1c.[71] Additionally, intervention characteristics such as group sessions, contact with an expert/professional, supervised physical activity were considered effective. Specific combinations of behaviour change techniques may also be more effective than others, and could thus also be considered.[69]

Personalized health for prevention and management of type 2 diabetes

Due to the known heterogeneity of type 2 diabetes several subtyping methods have been proposed, ranging from pathophysiology based phenotyping to completely data-driven strategies.[39,72–75] While some of these subtyping methods show differential risk of diabetes-related complications among subgroups, or provide some direction for precision medicine,

little has been described about the potential of such subtyping approaches for personalized treatment with lifestyle interventions. There are however indications that the efficacy of lifestyle interventions may be partly determined by the level of insulin resistance in the liver and skeletal muscle as well as the level of beta-cell function. Research showed that in individuals with obesity and type 2 diabetes, short-term aerobic training is mainly effective in improving peripheral insulin sensitivity, rather than hepatic insulin sensitivity.[76] Additionally, meta-analyses have shown that both aerobic and resistance training are effective in reducing hyperglycemia in individuals with type 2 diabetes; with hyperglycemia being mainly related to muscle insulin sensitivity.[22] These positive effects of exercise on insulin sensitivity and responsiveness of glucose disposal are probably due to exercise-induced adaptations in the muscle.[77] A few studies on the effectiveness of personalized physical activity interventions for type 2 diabetes have shown promising results, but were limited to personalized advice based on current behaviour and did not include information on diabetes phenotype.[78,79] In terms of nutrition, a post-hoc analysis of the CORDIO-PREV-DIAB study showed that individuals with mainly muscle insulin resistance benefitted more from a Mediterranean diet as measured by an improvement in the disposition index, a measure of beta-cell function, whilst individuals with mainly hepatic insulin resistance experienced a more pronounced increase in disposition index on a low-fat, high-complex-carbohydrate diet.[80] A post-hoc analysis of the LIPGENE study showed that individuals with higher insulin resistance benefitted to a greater extend from the replacement of saturated fatty acids by high-monounsaturated fatty acids and low-fat, high complex carbohydrate diets as compared to those with lower baseline insulin resistance.[26] Contrastingly, individuals with a lower insulin resistance may be more prone to the adverse effects of saturated fatty acids. Thus, adhering to the dietary guidelines for saturated fat may be even more important in the prevention of type 2 diabetes. In addition, studies have also shown beneficial effects of meals or diets high in MUFA on postprandial insulin excursions and total and hepatic insulin sensitivity as compared to meals high in saturated fatty acids or a control diet.[81–83] A recent study investigating 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.[84] For people who are predominantly at risk of developing type 2 diabetes due to reduced beta-cell capacity dietary advice targeted at avoiding large glycemic fluctuations may be particularly beneficial.[85] In terms of physical activity, it seems that moderate intensity exercise reduces risk of developing type 2 diabetes, especially for people with low initial levels of physical activity.[86]

Continuous data for personalized health

So far, most personalized nutrition or personalized lifestyle approaches measure health status of participants once and subsequently determine personalized advice. However, to account for changes in health and lifestyle as a result of the personalized interventions or other factors,

and to ensure that personalized recommendations fit the current situation of an individual, repeated measurements are required.[48,65] Rapid developments in the field of mobile technologies, wearables and sensors may allow for real-time collection and feedback on lifestyle and health data.[87] Evidence is mounting that individuals indeed differ in terms of dynamic responses to lifestyle as quantified by continuous glucose monitoring. Several studies have for instance shown that the postprandial responses to food differ greatly between individuals.[53,88,89] Additionally, research has shown that glucose fluctuations in apparently healthy people are highly heterogeneous, and subtypes based on specific patterns of glycaemic responses reflect variable underlying physiology.[90] Studies have also shown that continuously measured glucose values can be used to predict future glucose values with decent accuracy,[91] which provides opportunities for more real-time feedback on the effects of lifestyle on glucose values.

Implementation of evidence-based personalized lifestyle approaches

Understanding the potential of personalized lifestyle interventions for the prevention and management of type 2 diabetes, also requires insight in the feasibility and effectiveness of implementing such interventions in real-life. Several aspects that need to be considered when implementing a personalized lifestyle approach in general, or in the context of type 2 diabetes, have been described.[37,48] These include the need for accurate and validated, but also user-friendly measurements, careful consideration of ethics and privacy issues, and the need for rigorous scientific evidence for the underlying food-health relations, models and health effects of personalized lifestyle interventions. Additionally, equity should be considered when developing personalized lifestyle interventions, which also requires making a good trade-off between the added value of health measurements, such as -omics techniques, and their costs.[37] On top of these considerations, to investigate the potential of personalized lifestyle approaches in real-life, these should also be studied in real-world settings.[92] Real-world settings are contexts where health research findings are applied in practice and include primary healthcare, but also the work or home environment. Although field-lab studies may be less controlled as compared to traditional randomised controlled trials, such studies provide essential insights in the feasibility and (clinical) impact of lifestyle interventions in real-life.[93]

Outline of this thesis

There is some evidence for beneficial effects of personalized nutrition or personalized physical activity, but this field is still in its infancy. More research is needed to investigate if personalized lifestyle is effective in the prevention and treatment of type 2 diabetes. Additionally, most studies up to now focused either on phenotype or genotype-based lifestyle recommendations, or recommendations based on current behaviour and behaviour change support. There have been only a few studies investigating the effects of a more holistic personalized lifestyle intervention on dietary behaviour and metabolic health status. To

investigate the feasibility and potential of personalized lifestyle approaches, it is worthwhile to perform studies in a real-life setting. Lastly, little is known about the potential of continuous glucose monitoring combined with lifestyle data to allow for more real-time feedback and advice in optimizing glycaemic control in prevention or treatment of type 2 diabetes. Therefore, in this thesis we aim 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 in a real-life setting. Herein, we will first investigate the effectiveness of a holistic personalized lifestyle approach as compared to generic dietary advice in optimizing health status and preventing type 2 diabetes. Secondly, we will investigate the effectiveness and feasibility of a personalized lifestyle approach based on type 2 diabetes pathophysiology (diabetype) for ameliorating the disease in primary care. Lastly, the potential of continuously measured glucose values for personalized lifestyle advice will be investigated, and if diabetypes can be used for such personalization.

The first two chapters of this thesis describe effects of personalized lifestyle advice as compared to generic advice in the prevention of lifestyle-related diseases. In **Chapter 2** we evaluate whether personalized lifestyle advice combined with behaviour change support improves wellbeing in a relatively healthy senior population, as compared to generic lifestyle advice. In **Chapter 3** we investigate the impact of a 10-week personalized systems nutrition program, including personalization based on phenotypic, genotypic and lifestyle data as well as behaviour change guidance, on lifestyle behaviour and health outcomes in a real-life work-setting. The next two chapters are focusing on the feasibility and effectiveness of personalized lifestyle approaches for ameliorating type 2 diabetes in a primary care setting. In these two studies a diabetes subtyping method based on the glucose and insulin response to an oral glucose tolerance test and subsequently calculating the level of muscle insulin resistance, liver insulin resistance and beta-cell function is applied. The resulting diabetypes are used to tailor the lifestyle interventions for people with type 2 diabetes. In **Chapter 4** we assess the effectiveness of this subtyping approach and subsequent personalized lifestyle treatment in ameliorating type 2 diabetes in people with newly diagnosed type 2 diabetes in a primary care setting. In **Chapter 5** we investigate the feasibility and effectiveness of a holistic lifestyle intervention program, combining a 360 degrees diagnosis, diabetyping, behavioural change support and tailored treatment for people with more advanced type 2 diabetes. We investigate the effects of this personalized program in ameliorating type 2 diabetes, as well as the effects on the underlying pathophysiology.

To explore the usability of continuous data for personalized lifestyle advice in **Chapter 6** we describe a proof-of-principle study to predict and explain continuously measured glucose levels in healthy individuals using contextual factors, such as sleep, activity, and diet. Additionally, we use continuously measured glucose data to retrospectively predict meal moments. Ultimately, insights generated in this study could be used to develop self-management tools for the prevention of type 2 diabetes. In **Chapter 7** we apply continuous

monitoring in a population with type 2 diabetes. Here we assess the direct effects of four different lifestyle interventions on metrics of glucose profiles, including mean glucose, glucose excursions and glucose variability. Also, we investigate if a differential effect of lifestyle interventions on glucose metrics can be explained by the diabetes phenotype.

In **Chapter 8** we zoom in on the lessons learned regarding personalization of dietary recommendations, and specifically for the selection of input parameters, reasoning algorithms ranging from knowledge driven to data-driven and the resulting output, i.e., the communication of feedback on health status and dietary advice. This is done using the 'sense, reason, act' framework.

Lastly, in **Chapter 9** the main results and conclusions of the research performed as part of this thesis is discussed, and directions for future research are provided.

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