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

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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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2

BENEFICIAL EFFECT OF PERSONALIZED LIFESTYLE ADVICE COMPARED TO GENERIC ADVICE ON WELLBEING AMONG DUTCH SENIORS – AN EXPLORATIVE STUDY

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ABSTRACT

The aim of this explorative study is to evaluate whether personalized compared to generic lifestyle advice improves wellbeing in a senior population. We conducted a nine-week single-blind randomized controlled trial including 59 participants (age 67.7 ± 4.8 years) from Wageningen and its surrounding areas in the Netherlands. Three times during the intervention period, participants received either personalized advice (PA), or generic advice (GA) to improve lifestyle behavior. Personalization was based on metabolic health measurements and dietary intake resulting in an advice that highlighted food groups and physical activity types for which behavior change was most urgent. Before and after the intervention period self-perceived health was evaluated as parameter of wellbeing using a self-perceived health score (single-item) and two questionnaires (Vita-16 and Short Form-12). Additionally, anthropometry, and physical functioning (short physical performance battery, SPPB) were assessed.

Overall scores for self-perceived health did not change over time in any group. Resilience and motivation (Vita-16) slightly improved only in the PA group, whilst mental health (SF-12) and energy (Vita-16) showed slight improvement only in the GA group. SPPB scores improved over time in both the PA and GA group. PA participants also showed a reduction in body fat percentage and hip circumference, whereas these parameters increased in the GA group. Our findings suggest that although no clear effects on wellbeing were found, still, at least on the short term, personalized advice may evoke health benefits in a population of seniors as compared to generic advice.

1. INTRODUCTION

Physical activity and a healthy diet are lifestyle behaviors that significantly contribute to the prevention of chronic diseases and obesity [1-4]. In the Netherlands, more than 55% of the population has been classified as being insufficiently active [5] and over 35% reported sedentary behavior of 7–16 hours per day [6]. In the senior population in Europe the percentage of people being insufficiently active and reporting high sedentary behavior (13.3%) is even higher as compared to the adult population (8.5 – 9.6 %). In terms of dietary behavior, the Dutch National Food Consumption Survey showed that from 2007-2010 only 12-14% of the Dutch senior population met the recommended intake for vegetables and 17-26% met the recommended intake for fruit [7]. This survey also showed that more than 90% of the senior population exceeded the upper limit for saturated fat intake. These findings indicate a need for improvement in lifestyle behaviors among seniors that benefit public health.

Improving lifestyle requires a change in behavior. Previous studies show that personalized feedback and advice are more effective for improving dietary patterns and increasing physical activity than providing general information [8-14]. Personalization entails that feedback and advice are tailored to one individual, based on his or her characteristics. A potential reason that personalization is effective, is that people are more likely to pay attention to information that is relevant for them, and thus the impact of that information increases. Furthermore, in general people underestimate the likelihood that negative live events happen to them [15]. This optimistic bias could potentially be influenced by personalized information based on parameters that give an objective health risk indication like body weight, body fat percentage, food intake, but also genetic profiles.

In the current study, a holistic approach of personalization of lifestyle advice is adopted that encompasses tailoring the content of the advice (which information should be included in the message?), but also tailoring the form of the advice (how should the message be communicated?) and providing behavioral change support (how can the individual be aided in implementing the advice?). The content of the advice will be personalized based on previous investigations from the Food4Me research consortium including an array of lifestyle, phenotypic and genetic data which is fed back to the individual in prescription for action (16, 17). It was previously demonstrated that dietary advice tailored to an individual's health status is more effective for improving health parameters as compared to a generic advice [18-21].

The form in which advice is communicated has a pivotal role in changing behavior. Relevant insights from social psychology and marketing research are therefore needed to compose personal feedback for consumers that is effective in helping them to choose and maintain an optimal lifestyle. For example, actual behavior change can be aided by setting clear and achievable goals, for instance by forming "if-then plans" or "implementation intentions"

[22]. Social Cognitive Theory [23]) gives insight into how individuals regulate their behavior to achieve goals that can be maintained over time. An important aspect of this theory is self-efficacy, which is defined as the extent to which one believes in her or his own ability to reach a certain goal[24]. Since personalized lifestyle advice is a tool to help individuals regulate or change their lifestyle behaviors, the degree to which a person feels capable to implement a lifestyle advice determines the extent to which an individual will ultimately initiate and maintain behavior change [24]. In addition, some participants like to choose from many options to adapt their behaviors, whereas others are satisfied with only a few choice options. People with a lower tendency to maximize their choice are better off with less options [25]. As a result, the preferred number of healthy alternative options offered in a personalized advice may be something that varies per person and should in that sense be personalized too. Previous research established these individual differences in choice maximization (Maximization scale) [25, 26]. Considering these personal preferences and formulating realistic goals that fit within the current lifestyle can help individuals to realize behavior change.

As indicated, a potentially interesting target group for personalized advice for improving dietary behavior and physical activity are elderly people. It is estimated that 30% of seniors older than 60 years and >50% of seniors older than 80 years suffer from progressive loss of muscle mass and function [27-29]. At the same time, there is a high prevalence of overweight and obesity among seniors in the Netherlands, i.e., 60% [30]. Both obesity and age-related decline in muscle mass, strength and functional abilities can be counteracted with a healthy diet and regular physical exercise [28].

To our knowledge, combining data on individual behavior, health status and genetics to generate personalized lifestyle advice has only been used in a limited number of studies [31, 32]. Even less so for studies taking a holistic approach towards personalized nutrition by also including socio-psychological factors and/or behavior change techniques in personalized advice systems [14, 17]. In addition, personalized lifestyle advice for optimizing muscle health in seniors has not been studied before. It is thus unknown whether a senior population is open to personalized lifestyle advice and towards applying such advice in daily life.

In summary, the current study is explorative in nature and its primary focus is to evaluate whether personalized as compared to generic lifestyle advice improves wellbeing of participants in terms of self-perceived health (primary outcome) and objective biological health measures (secondary outcome). Lifestyle advice will be tailored based on dietary intake, genotype, phenotype, and measures of muscle health as well as socio-psychological factors via decision trees that are developed for this study. Additionally, participants will be given support in implementing the personalized advice through the formulation of implementation intentions. As an additional outcome, this explorative study will provide insight in the acceptance of personalized lifestyle advice by a senior population.

2. MATERIALS AND METHODS

2.1. Study participants

Study participants were recruited from the SenTo panel, a consumer panel of Wageningen University and Research, consisting of more than 800 seniors, as described elsewhere [33]. SenTo members aged 60 years and over received an invitation for study participation. Those willing to participate completed a screening questionnaire. Seniors were eligible to participate in the study when they: 1) were ≥ 60 years of age; 2) reported sedentary behavior for at least 10 hours a day; 3) were in good health and 4) had a self-reported BMI of 20-30 kg/m^2. Seniors were excluded from participation when they: 1) used medication known for its effects on blood glucose, cholesterol or insulin; 2) had a history of medical or surgical events including physical limitations, cardiovascular events or cerebrovascular accident, 3) were rehabilitating; 4) had a pacemaker, 5) suffered from diabetes type I or type II; 6) were on a specific diet (slimming or prescribed diet); 7) had physical, mental or practical limitations in using computerized systems; 8) had an alcohol consumption > 28 units/week for males and > 21 units/week for females or 9) experienced unintended weight loss or weight gain of > 2 kg in the three months prior to the screening. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of Wageningen University (METC-WU 15/12; NL53218.081.15, date of approval 28-08-2015) and was registered in the Dutch Trial Register (NTR5490). This study was conducted in accordance with the Declaration of Helsinki.

2.2. Study design

The explorative study was designed as a parallel randomized controlled trial with an intervention period of nine weeks. A period of nine weeks seems to be sufficient to evaluate the initiation of behavior change [34] as well as of physical health changes (35-39). Participating seniors were not informed about the purpose of the study (single-blind). Participants were randomly allocated to either the intervention group or the control group balanced for gender, muscle health (i.e., hand grip strength) and socio-psychological factors (i.e., individual differences in choice maximization). Both at baseline and at the end of the intervention period well-being was assessed even as biological health parameters. After the intervention period, satisfaction with the received advice was evaluated using a combination of multiple-choice and open-ended questions. Subjects were informed about the actual purpose of the study, immediately after the last test session.

Besides wellbeing and the biological health parameters reported on here, also PhenFlex challenge tests (standardized liquid mixed meal) were conducted to assess phenotypic flexibility as a measure of health. These results were not used as input for the personalization of dietary advice and will be presented elsewhere.

2.3. Control treatment: Generic advice

At the start of the intervention period, participants received feedback on their health status based on extensive baseline measurements. Subsequently, the control group (n=29) received Generic Advice (GA) for improving their muscle health, using a leaflet with the national food-based dietary guidelines as published by the Netherlands Nutrition Centre [40]. This leaflet contained guidelines on the consumption of five categories of basic food products: 1-fruit and vegetables; 2-potatoes, bread, rice, and pasta; 3-dairy, meat, fish, and meat replacement products; 4-low-fat margarines, margarines, and oils; 5-water, as well as generic guidelines for an active lifestyle, meaning at least 30 minutes of physical activity per day.

2.4. Intervention treatment: Personalized advice

At the start of the intervention period, participants received feedback on their health status based on extensive baseline measurements. Subsequently, the intervention group (n=30) received the same leaflet with food-based dietary guidelines as the GA group. In addition, they received personalized advice (PA) through an online portal. The PA promoted muscle health among seniors and was in line with national and international recommendations provided by the Health Council of the Netherlands, the Netherlands Nutrition Centre and International expert groups. The personalized advice was based on the food based dietary guidelines as stated in the generic advice, and resulted in a set of nine personalized advice, of which seven focused on diet (intake of protein, energy, saturated fat, omega-3 fatty acids, salt, vitamin D and liquid not including alcohol) and two focused on physical activity (aerobic and resistance exercise). The content of the nine PA for each participant was determined with nine different underlying decision trees incorporating biological personalization factors outlined in **Table 1**. The cut-off values for each personalization factor as reported in **Table 1** determined which advice was given. Every PA included a green, orange, or red emoji (of a smiling face) that indicated whether the need for behavior change on that aspect was low, moderate, or high. Participants were instructed to formulate implementation intentions [22] in which they described how they planned to apply at least two of the received advices, preferably those advices indicated by an orange or red emoji, using a digital questionnaire with choice menus for time, situation and action. For example, participants had to indicate at which time of the day (e.g., in the evening) and in which situation (e.g., when I watch television) they were planning to replace an unhealthy product that they reported in their 3-day food diary (e.g., crisps) by a healthier product (e.g., whole meal cracker). Based on their personal preference for either many or a few choice options (choice maximization) participants were presented with either 3 or 10 healthy alternatives for the unhealthy product. Healthy alternatives were based on the Dutch Food Database [41].

Table 1: *Biological factors and cut-off values used to personalize lifestyle advice.*

Generic advice	Personalization factor	Classification	Personalization based on SNP	Classification
Protein intake	protein intake[a] BMI, glucose, cholesterol, triglycerides, blood-pressure	recommended (≥1.2 g/kg BW), low (0.52-1.2 g/kg BW), very low (≤0.52 g/kg BW) metabolic healthy; metabolic unhealthy[b]		
Energy intake	BMI waist circumference physical activity energy intake[a]	underweight (<18 kg/m^2), normal (18-30 kg/m^2), overweight/obese (>30 kg/m^2) normal (M<94 cm, F <80 cm), high (M ≥ 94 cm, F ≥ 80 cm) recommended (≥30 min), low (<30 min); recommended (low physical activity: M <2300 kcal, F <1900 kcal; normal physical activity: M <2600 kcal, F <2100 kcal), high (low physical activity: M ≥2300 kcal, F ≥1900 kcal; normal physical activity: M ≥2600 kcal, F ≥2100 kcal)	SNP rs9939609 - gene FTO	risk (AA / TA), non-risk (TT)
Saturated fat intake	fat intake[a]	recommended (≤10% of total energy intake), high (>10% of total energy intake)	SNP rs7903146 – gene TCF7L2	risk (TT/CT), non-risk (CC)
Fish intake	omega-3 fatty acid intake[a]	recommended (≥0.6% of total energy intake), low (<0.6% of total energy intake)	SNP rs174546 - gene FADS1	risk (CC), non-risk (TT/TC)
Liquid intake	age liquid intake[a]	<70 y, ≥70 y recommended (age <70 y: ≥1.5 L, age ≥70 y: ≥1.7 L); low (age <70 y: <1.5 L, age ≥70 y: <1.7 L)		

Generic advice	Personalization factor	Classification	Personalization based on SNP	Classification
Salt intake	blood pressure salt intake[a]	recommended (SBP <130 mmHg AND DBP <85 mmHg), high (SBP ≥130 mmHg OR DBP ≥85 mmHg) recommended (≤6 g/day), high (>6 g/day)		
Vitamin D intake	vitamin D intake[a]	recommended (≥10 mcg/day) vs low (<10 mcg/day)	SNP rs731236 - gene VDR taq1	risk (CC), non-risk (CT/TT)
Endurance training	SPPB score	low (0-4), medium (5-8), high (9-12)	SNP rs4341 - rs4343 - gene ACE. SNP rs143383 - gene GDF5	risk (LL), non-risk (DD). risk (CT/TT), non-risk (CC)
Resistance training	hand grip strength	low vs normal[c]	SNP rs4341 - rs4343 - gene ACE. SNP rs143383 - gene GDF5	risk (LL), non-risk (DD). risk (CT/TT), non-risk (CC)

SNP, single nucleotide polymorphism; BW, body weight; M, Males; F, females; SBP, systolic blood pressure; DBP, diastolic blood pressure; [a] Intake values are estimated from food diaries; [b] Metabolic unhealthy is defined as increased waist circumference (M ≥ 94 cm; F ≥ 80 cm) or BMI >30 kg/m^2 combined with either increased fasting triglycerides (≥150 mg/dL) or decreased HDL-cholesterol (M ≤ 1,03 mmol/L, F ≤1,28 mmol/L) or increased blood pressure (systolic ≥130 mmHg OR diastolic ≥85 mmHg) or increased fasting glucose (≥5.6 mmol/L). [c] Cut-off values for hand grip strength are age and gender specific based on meta-analysis by Bohannon et al. [42]

Twice during the intervention period, the intervention group received an updated version of the PA considering potential changes in dietary behavior (weeks 4 and 7).

2.5. Biological measurements for health feedback

Biological measurements were performed at baseline (T=0) to quantify individual health status to be used in feedback for subjects in both groups (PA + GA) and as input for the decision trees to determine the content of the PA. Participants came to the research facility after an overnight fast. Upon arrival, first some saliva was collected using a buccal swab, to determine the genetic profile (the following SNPs were included: FADS1 rs174546, TCF7L2 rs7903146, FTO rs9939609, VDR-taq1 rs731236, ACE rs4341, ACE rs4343, GDF5 rs143383). Subsequently, finger-stick blood samples were collected from each participant to assess fasting glucose (Medisana MediTouch 2 glucose meter), triglycerides and cholesterol (Mission 3-in-1 cholesterol meter). Blood pressure was measured three times (Medisana MTX). The average blood pressure of the last two measurements was considered for data analysis. All these measurements were performed under supervision of a study nurse. To

further characterize muscle health, participants performed the Short Physical Performance Battery (SPPB), which includes a set of physical tests (gait speed, chair stand and balance tests) [43]. SPPB scores can range from 0 (worst performance) to 12 (best performance). Both the total score and the scores on the individual tests were recorded. In addition, handgrip strength was measured using an isometric hand dynamometer (JAMAR, Sammons Preston). The best of three attempts for the left and the right hand yielded the final score for hand grip strength. Body fat percentage was measured with a Tanita weighing scale with bioelectrical impedance measured from leg to leg [44]. Anthropometric data including height, body weight, waist-, hip-, arm- and thigh-circumference were collected by a trained research assistant using standard operation procedures at baseline and at the end of the study period (T=0 and T=1). At baseline and every three weeks throughout the intervention period participants recorded their food intake via a digital food diary on two weekdays and one weekend day (MijnEetmeter, Netherlands Nutrition Centre). From this diary we obtained estimates for intake of calories, protein, vitamin D, saturated fat, omega-3 fatty acids, salt, and liquid. A physical activity tracker was provided to the participants for monitoring their daily physical activity. However, due to a lot of technical problems with the device, it was removed from the study after the first advice.

2.6. Self-perceived health

Both at baseline and at the end of the intervention period, self-perceived health was evaluated with a single-item question (self-perceived health score) and further specified with the Dutch translation of the Short-Form 12 (SF12) [45] and the Vita-16, a short questionnaire addressing the core dimensions of vitality: energy (Cronbach's $\alpha = .84$), motivation (Cronbach's $\alpha = .92$) and resilience (Cronbach's $\alpha = .92$) [45]. *2.7 Socio-psychological factors*

At baseline, all participants completed a questionnaire that included the shortened Maximization Scale (8 items, 7-points Likert-scale, Cronbach's $\alpha = .83$) based on Nenkov et al. [26]. Based on the median score of the Maximization scale we split the intervention group in those with preference for many choice options when formulating implementation intentions (i.e., 10) and those with preference for few options (i.e. 3).

Self-efficacy towards eating proteins (6 items, 7-points Likert scale, Cronbach's $\alpha = .97$) and self-efficacy towards exercise (6 items, 7-points Likert scale, Cronbach's $\alpha = .94$) were evaluated at T=0 and T=1 with a questionnaire based on Strecher et al. [47]. For these multi-item scales, combined scores were calculated by averaging the individual items. The translated and backwards translated versions of the questionnaire have been used and tested in previous studies, except for some specific items. These items are adjusted to measure factors specifically for this study. Pre-tests have been conducted to determine whether the adjusted items are interpreted as they were intended.

2.7. Quantitative and qualitative evaluation

To evaluate compliance with the advice, two weeks after each PA, participants in the PA group were asked to report to what extent they applied their formulated implementation intentions on a 7-points Likert scale. At the end of the intervention period, all participants received a questionnaire to report on compliance with the food based dietary guidelines (7-points Likert scale) and perceived healthiness of the diet (10-points structured line scale). Acceptance of the PA including tools and measurements was evaluated with open and multiple-choice questions.

2.8. Statistical analysis

All analyses were performed with SPSS, version 25.0. Due to the explorative nature of the study and the small size of the sample, we refrained from using statistical difference tests. Instead, we decided to report the mean estimates together with the confidence intervals (CIs). Doing so allows us to obtain an indication of the precision of the sample means and their differences while avoiding the flaws accompanied with using statistical difference tests [48]). Baseline characteristics of participants in the PA and GA group were compared and changes over time (T1 vs T0) were examined.

3. RESULTS

3.1. Baseline characteristics

Table 2 shows baseline characteristics of participants. A total of 59 participants (22 males, 37 females) with a mean age of 67.7 ± 4.8 years were included in the study. Confidence intervals of the mean differences in characteristic between the intervention (PA) and control group (GA) include 0, indicating that the two groups were similar at baseline. Mean BMI (based on height and body weight measured at the research facility) was 26.1 kg/m^2, thus slightly above the recommended upper level of 24.9 kg/m^2. Self-reported BMI was used to select participants (20-30 kg/m^2), but at baseline BMI turned out to be higher than 30 for 9 participants. Mean reported sedentary behavior was 12.5 hours a day. In general, mean nutrient intakes at baseline were in line with dietary reference values except for saturated fat, salt and vitamin D. Intake of saturated fat and salt exceeded the recommended maximum intake of respectively 20 and 6 grams per day as stated on the website of the Netherlands Nutrition Centre (http://www.voedingscentrum.nl). Mean vitamin D intake was below the recommended daily intake of 10 mcg; however, supplement intake was not recorded. For the socio-psychological measures, scores on the 7-point composite scales were above the midpoint of the scale, except for the maximization scale (**Table 2**). This implies that participants reported relatively high self-efficacy regarding protein intake (mean = 6.05) and exercising (mean = 5.61). Mean score on the maximization scale was below the midpoint of

the scale (mean = 3.08), indicating that participants are generally satisfied with a limited number of choice options.

Table 2: *Baseline characteristics of study population* [a]

	Total study population (N= 59)[b]	**Generic advice (GA) (N = 29)**[b]	**Personalized advice (PA) (N = 30)**[b]	**Mean difference, 95% CI**
Age	67.7 (4.8)	67.4 (4.25)	68.0 (5.38)	-0.6 [-3.1, 2.0]
Age (range)	60 – 79 years	61-75 years	60-79 years	-
Gender:				
Male (%)	37.3%	37.9%	36.7%	-
Female (%)	62.7%	62.1%	63.3%	
BMI[c]	26.1 (3.2)	26.0 (3.4)	26.1 (3.0)	0.0 [-0.3, 0.2]
BMI (range)[c]	20.1-32.8	20.1-32.8	21.4-31.4	-
Calorie intake (kcal/day)	1825 (510)	1790 (472)	1852 (545)	-61.7 [-344.1, 220.8]
Protein intake (g/day)	80.1 (21.2)	82.9 (23.2)	77.9 (19.6)	5.0 [-6.7, 16.7]
Saturated fat intake (g/day)	26.1 (11.8)	27.1 (11.5)	25.3 (12.1)	1.8 [-4.7, 8.3]
Omega-3 fatty acid intake (mg/day)	1.4 (1.0)	1.4 (0.9)	1.5 (1.1)	-0.1 [-0.6, 0.4]
Salt intake (g/day)	6.1 (2.2)	5.9 (1.9)	6.2 (2.4)	-0.4 [-1.5, 0.8]
Vitamin D intake from foods (mcg/day)	2.4 (1.5)	2.5 (1.4)	2.3 (1.7)	0.1 [-0.7, 1.0]
Liquid intake (L/day)	2.0 (.7)	2.0 (.7)	2.0 (.8)	0.0 [-0.4, 0.4]
Maximization Scale[d]	3.1 (1.2)	3.2 (1.3)	3.0 (1.0)	0.2 [-0.5, 0.8]
Self-efficacy regarding exercising[d]	5.6 (1.1)	5.5 (1.1)	5.7 (1.1)	-0.3 [-0.8, 0.3]
Self-efficacy regarding eating proteins[d]	6.1 (.9)	6.0 (1.0)	6.1 (1.0)	-0.1 [-0.6, 0.4]

a Data are reported as mean (SD) unless indicated differently; CI = confidence interval; b N varies between variables due to missing data; c BMI based on clinical measurements; d Answering scales range from 1 to 7

3.2. Personalized advice

Figure 1 shows how many participants in the PA group received a green, orange, or red emoji for the first (week 1) and last advice (week 7), i.e., how many participants demonstrated respectively a low, moderate, or high need for behavior change for that specific item. Need for behavior change with respect to physical activity in terms of endurance and resistance training was low to moderate for most participants in the PA group. This also applies to liquid

intake and to a lesser extent to salt and protein intake. At baseline, need for behavior change with respect to general guidelines about calorie intake, saturated fat intake, omega-3 fatty acid intake and vitamin D intake was high for about half of the study participants, indicating a scope for improvement. Such improvement was observed for omega-3 fatty acids; the PA compliance with the final advice on omega-3 fatty acids was good for almost all participants. Adherence to general guidelines about intake of saturated fat and liquids also improved during the intervention period. Despite the focus on muscle health in this study and a high number of formed implementation intentions for protein intake at baseline (n=14), protein intake worsened during the study, with more participants receiving an orange emoji and less participants receiving a green emoji. Next to protein intake, participants in the intervention group often formulated implementation intentions for improving vitamin D intake (n=19), calorie intake (n=13), and saturated fat intake (n=10).

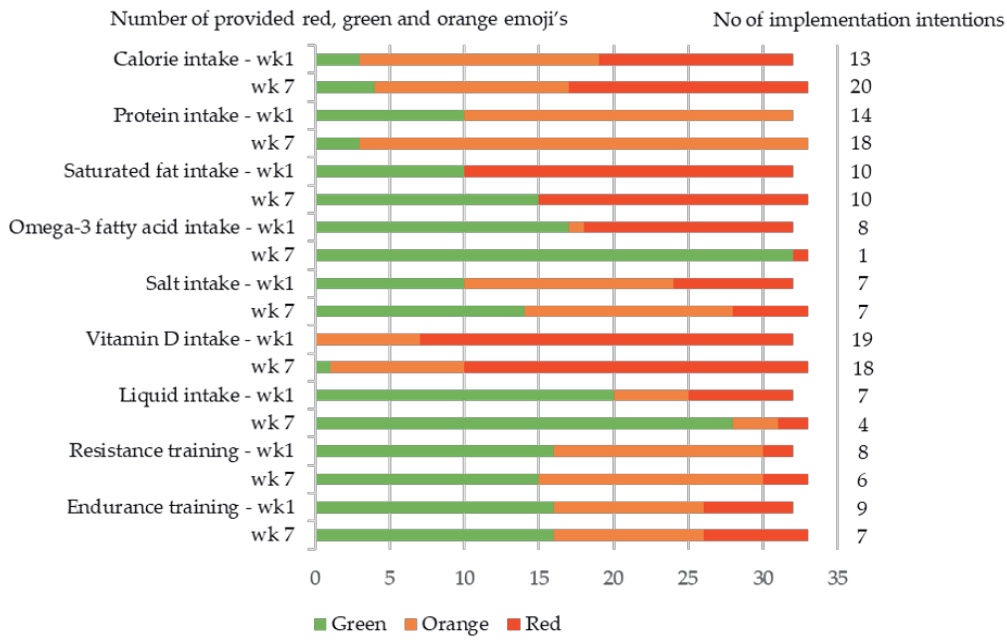

Figure 1*: Need for behavior change in the PA group: number of participants receiving green, orange, and red emoji per advice at first (wk1) and last (wk7) personalized advice moment.*

3.3. Self-perceived health and self-efficacy

Table 3 shows mean scores and corresponding CIs on self-perceived health measures (self-perceived health score, SF12 and Vita-16) at baseline (T0) and at the end of the study period (T1). Also, the difference scores and their CIs between T0 and T1 are displayed in the table. These results show that most of the times scores did not improve over time as mean differences are around zero and CIs include zero. However, the mental health dimension of the Short-Form 12 and the energy sub-scale of Vita-16 increased for the GA group. In the PA

group scores for motivation and resilience (sub-scales of Vita-16) slightly improved over time. Self-efficacy regarding protein intake tends to decrease over the course of the intervention period for both the PA and GA group. This is in line with the decline of protein intake during the study. Self-efficacy regarding exercise shows no changes. The final column of Table 3 shows the mean differences and their CIs between the PA and GA group. The small mean differences and CIs including zero indicate no differences between the two groups, as is also indicated by the generally large overlap between the CIs of the GA and PA group.

3.4. Biological measurements

Table 4 shows changes in biological measurements during the intervention period. The mean scores and corresponding CIs in both the PA and GA group indicate that SPPB scores improved over time. Furthermore, the PA group showed a greater reduction in waist circumference. Note that regarding fat percentage and hip circumference we observe an opposite effect when comparing the GA to the PA group: fat percentage and hip circumference increases for the GA group, while these parameters decrease for the PA group. The final column of Table 4 shows the mean differences and their CIs between the PA and GA group. The small mean differences and CIs including zero indicate no differences between the two groups, as is also indicated by the generally large overlap between the CIs of the GA and PA group.

3.5. Quantitative and qualitative evaluation by participants

We observed no differences between the GA and PA group in perceived compliance with Dutch food based dietary guidelines (7-points-scale, GA: mean=5.26 ± 1.37; PA: mean=5.18 ± 1.01) and perceived healthiness of actual diet (10-points scale, GA: mean=7.26 ± 1.76; PA: mean=7.68 ± 1.09) at the end of the study. The PA group indicated they increased their awareness, knowledge, and insight in individual health behaviors. Mean self-reported compliance with the formulated implementation intentions was 4.86 (7-points scale, SD=1.46). Some participants (n=8) experienced difficulties with the digital food diary, especially the user friendliness of the application had a low score (2.4 on a 7-points scale). In general, all participants evaluated the study as very positive and all, but one indicated they would participate again.

***Table 3**: Changes in self-reported health measures over time within and between groups*

	Generic advice (N = 29)	**Personalized advice (N = 30)**	**Mean difference**
Self-perceived health (1-5) T0	3.5 [3.2, 3.7]	3.5 [3.3, 3.8]	0.0 [-0.4, 0.3]
T1	3.5 [3.2, 3.8]	3.4 [3.1, 3.7]	0.1 [-0.3, 0.5]
Difference T1-T0	0.0 [-0.1, 0.2]	-0.1 [-0.4, 0.2]	0.2 [-0.2, 0.5]
SF12_Physical health (0-100) T0	51.0 [48.0, 54.1]	49.7 [47.1, 52.4]	1.5 [-2.4, 5.4]
T1	50.9 [48.5, 53.2]	49.6 [47.0, 52.2]	1.3 [-2.2, 4.7]
Difference T1-T0	-0.2 [-3.3, 2.9]	-0.2 [-2.4, 2.1]	0.0 [-3.7, 3.7]
SF12_Mental health (0-100) T0	52.2 [48.8, 55.6]	54.9 [52.0, 57.8]	-2.5 [-6.8, 1.8]
T1	54.4 [51.4, 57.4]	54.2 [52.1, 56.4]	0.2 [-3.4, 3.7]
Difference T1-T0	2.2 [0.0, 4.4]	-0.7 [-3.1, 1.7]	2.9 [-0.2, 6.1]
Vita16_Energy (1-7) T0	5.2 [4.6, 5.7]	5.5 [5.1, 5.8]	-0.2 [-0.9, 0.4]
T1	5.6 [5.2, 6.0]	5.5 [5.1, 5.9]	0.1 [-0.4, 0.7]
Difference T1-T0	0.4 [0.0, 0.9]	0.0 [-0.3, 0.3]	0.4 [-0.1, 1.0]
Vita16_Motivation (1-7) T0	5.4 [4.8, 5.9]	5.3 [4.9, 5.7]	0.0 [-0.6, 0.7]
T1	5.6 [5.3, 5.9]	5.7 [5.3, 6.0]	0.0 [-0.5, 0.4]
Difference T1-T0	0.3 [-0.2, 0.8]	0.3 [0.0, 0.7]	-0.1 [-0.6, 0.5]
Vita16_Resilience (1-7) T0	5.3 [4.8, 5.8]	5.2 [4.7, 5.6]	0.2 [-0.5, 0.8]
T1	5.6 [5.3, 5.9]	5.6 [5.3, 5.9]	0.0 [-0.4, 0.5]
Difference T1-T0	0.3 [-0.2, 0.8]	0.4 [0.1, 0.8]	-0.1 [-0.7, 0.5]
Vita16_Overall vitality (1-7) T0	5.3 [4.8, 5.8]	5.3 [5.0, 5.7]	0.0 [-0.6, 0.6]
T1	5.6 [5.3, 5.9]	5.6 [5.3, 5.9]	0.1 [-0.4, 0.5]
Difference T1-T0	0.4 [-0.1, 0.8]	0.2 [0.0, 0.5]	0.1 [-0.4, 0.6]
Self-efficacy_exercise (1-7) T0	5.4 [4.8, 5.9]	5.6 [5.2, 6.1]	-0.2 [-0.8, 0.3]
T1	5.2 [4.6, 5.9]	5.4 [4.9, 5.8]	-0.1 [-0.8, 0.5]
Difference T1-T0	-0.2 [-0.8, 0.4]	-0.3 [-0.8, 0.2]	0.1 [-0.7, 0.9]
Self-efficacy_protein intake (1-7) T0	5.8 [5.4, 6.3]	6.2 [5.8, 6.6]	-0.1 [-0.6, 0.4]
T1	5.2 [4.7, 5.7]	5.6 [5.3, 6.0]	-0.3 [-0.9, 0.3]
Difference T1-T0	-0.6 [-1.2, 0.0]	-0.5 [-1.0, -0.1]	-0.1 [-0.8, 0.6]

Note: 95% CIs are reported in brackets.

***Table 4**: Changes in biological measures over time within and between groups*

	Generic advice (N = 29)	**Personalized advice (N = 30)**	**Mean difference**
SPPB (1-12) T0	10.3 [9.7, 10.8]	10.3 [9.7, 10.9]	-0.1 [-0.8, 0.7]
T1	10.7 [10.3, 11.1]	11.1 [10.7, 11.4]	-0.3 [-0.8, 0.2]
Difference T1-T0	0.5 [0.1, 0.9]	0.8 [0.3, 1.2]	-0.3 [-0.8, 0.3]
Fat (%) T0	31.5 [28.2, 34.8]	32.8 [30.0, 35.5]	-0.5 [-4.7, 3.6]
T1	32.1 [29.1, 35.0]	31.7 [28.4, 34.9]	0.6 [-3.6, 4.8]
Difference T1-T0	0.6 [-0.5, 1.7]	-1.1 [-2.3, 0.1]	1.7 [0.2, 3.3]
Waist (cm) T0	93.6 [88.8, 98.3]	93.4 [89.5, 97.2]	1.0 [-4.7, 6.7]
T1	93.2 [88.6, 97.7]	91.5 [87.5, 95.5]	2.3 [-3.3, 8.0]
Difference T1-T0	-0.4 [-1.6, 0.8]	-1.9 [-2.9, -0.8]	1.4 [-0.1, 2.8]
Hip (cm) T0	100.1 [97.2, 103.1]	101.0 [98.3, 103.7]	-0.4 [-4.2, 3.4]
T1	101.0 [98.2, 103.7]	99.9 [97.1, 102.6]	1.6 [-2.1, 5.2]
Difference T1-T0	0.8 [-0.3, 1.9]	-1.1 [-2.8, 0.6]	2.0 [0.0, 3.9]
BMI (kg/m^2)T0	25.8 [24.5, 27.0]	26.3 [25.2, 27.3]	-0.1 [-1.7, 1.6]
T1	25.8 [24.6, 27.1]	26.1 [25.0, 27.2]	0.1 [-1.5, 1.8]
Difference T1-T0	0.1 [-0.2, 0.3]	-0.1 [-0.3, 0.1]	0.2 [-0.1, 0.5]
Grip Strength			
Dominant Hand (kg) T0	32.6 [28.9, 36.3]	32.8 [29.4, 36.1]	0.6 [-4.2, 5.4]
T1	32.2 [28.4, 36.0]	32.8 [29.6, 36.0]	-0.4 [-5.2, 4.3]
Difference T1-T0	0.4 [-1.2, 2.0]	0.0 [-1.1, 1.1]	0.6 [-1.3, 2.5]

Note: 95% CIs are reported in brackets.

4. DISCUSSION

In this explorative study, we evaluated the potential of personalized lifestyle advice for improving wellbeing in a population of independently living, sedentary seniors. In this study, wellbeing was operationalized by self-perceived health as well as biological measures, including body composition, blood markers and physical function tests. Results showed that seniors receiving lifestyle advice over a period of nine weeks, either personalized or generic, improved physical function. In addition, there are subtle indications for potential beneficial health effects among those receiving PA. Our findings provide a cautious indication that on the short-term personalized advice may evoke additional health benefits in seniors as compared to generic lifestyle advices. Note that these findings are only applicable to our specific study population and cannot be translated to the general population.

4.1. General feedback for both GA and PA group

First, since all participants received feedback on their health status, monitored dietary intake and were equipped with an activity tracker, participants in both the GA group and the PA group were more aware of their individual (muscle) health and lifestyle behavior. Previous studies show that increased awareness of personal health status and behavior may induce behavior change, in terms of adhering to a healthier diet (when monitoring dietary intake) or increasing physical activity (when using an activity tracker) [49-53]. The motivation level of our study population was not evaluated, but probably relatively high as seniors were recruited from an elderly network that is regularly involved in studies on sensory evaluation and eating behavior. In addition, in general participants in lifestyle interventions seem to have a higher motivation for behavior change as compared to non-participants research [54]. Motivation to carry out a goal-directed behavior is a highly important success factor for behavior change interventions and therefore should be measured at baseline to allow better interpretation of the results [55]. Next to being motivated, however, the ability to translate this motivation into action is also key for successful behavior change. This is also referred to as self-regulation [56, 57]. Previous research demonstrated that self-regulation is important for initiating health-enhancing behaviors (e.g., consuming fruit and vegetables) and the inhibition of health risk behaviors (e.g., consuming products rich in saturated fat). However, as both types of behavior have different executive function determinants, being successful in initiating health enhancing behaviors does not automatically mean that an individual is successful in inhibiting risk behaviors too [58]. Further research on how to personalize dietary advice based on self-regulation determinants is recommended as self-regulation is highly relevant for compliance on the longer term.

4.2. Dietary advice for PA group and dietary behavior change

Among participants of the PA group, the behavior change needed was mainly the intake of calories, saturated fat, omega-3 fatty acids and vitamin D (red emoji) and the intake of protein (orange emoji) (Figure 2). This is in line with results from the Dutch food consumption survey among vital older adults showing that intake of saturated fat and salt exceeds recommended dietary intakes whereas the intake of whole meal products, fruit and fish is generally below the recommendation [59]. PA provided in our study was effective in improving adherence to dietary guidelines regarding saturated fat, omega-3 fatty acids, liquid, and salt. For improving intake of calories and vitamin D, the provided dietary advice seemed less effective, whereas for protein intake the PA even worsened adherence over time. This data was not available for the GA group and could therefore not be compared in terms of dietary behavior change over time. The effectiveness of the advice on the different dietary aspects may be related to the practical applicability of the advice as also demonstrated before by Sahyoun and colleagues [55]. For saturated fat, omega-3 fatty acids, liquid and salt, advice were related to the consumption of specific food groups (e.g., snacks, fish, drinks, processed foods) and probably relatively easy to implement in daily practice when motivated to change

behavior [607]. Implementation may be facilitated as consumers are able to recognize foods high in saturated fat and/or salt content and moreover, they are generally aware that foods high in salt or saturated fat content are not included in the food-based dietary guidelines [60]. Furthermore, front-of-pack labelling enhances attention to and facilitates the use of nutrition information on both dietary aspects [61-63]. In addition, many food manufacturers perform product reformulations to reduce saturated fat and/or salt content and thereby increased the availability of more healthy product variants. This also facilitates consumers in making healthy food choices.

Despite our observation that many participants formulated implementation intentions to optimize their calorie or protein intake, compliance with the PA advice did not improve throughout the study period. Advice on both dietary aspects might have been less straightforward, i.e., not related to specific food groups and therefore more difficult to implement into daily life than other dietary aspects, e.g., salt intake. Moreover, in our study consumers formulated one implementation intention per advice, meaning that they selected one type of food to be replaced by another. We chose this strategy as it has been suggested before that consumers can only handle a few behavior changes/implementation intentions at a time [64, 65]. To effectuate a meaningful change in protein or energy intake, replacing one food by a healthier alternative is likely to be insufficient. This means that to notice a change in protein or energy intake, either the study should have been implemented for a longer period or participants had to replace more products from their usual diet by alternative products in line with the PA based on available product information e.g., on food labels, besides the implementation intention formulated. This requires a high level of motivation to change behavior and understanding of nutrition information as also shown before [61, 66]. The complexity of the (personalized) advice on protein intake is also reflected in a decreased level of self-efficacy regarding protein intake in both the PA and the GA group at the end of the study as compared to baseline. Self-efficacy is a concept that is difficult to influence. In the literature there are inconsistent findings on the effect of an intervention on self-efficacy (e.g., 67, 68). This can be explained by the fact that the effect of a self-efficacy intervention depends on the technique used [69] and on the individual [70]. The loss in self-efficacy could also be due to participants experiencing this research as a reminder of their (unhealthy) diet, which might lead to a lack of confidence in someone's ability to succeed in following dieting advice and ultimately resulting in lower self-efficacy [68]. In their meta-analysis, Prestwich et al. [69] revealed that indeed emotional stress could undermine a positive effect on self-efficacy. Interventions that incorporate techniques that help to manage this stress were more successful in raising dietary self-efficacy than interventions that do not. We recommend future research in the context of personalized nutrition advice to also include some kind of stress management technique as part of the intervention.

Obtaining sufficient vitamin D from foods is difficult, especially for older adults, therefore the advice is to take daily supplements. However, the digital food diary we used in this study

did not record supplement use and therefore it is impossible to say something about compliance for this nutrient.

4.3. Health effects of personalized advice

Participants receiving PA had a stronger beneficial decline in body fat percentage, waist circumference and hip circumference than those receiving GA, although confidence intervals show a lot of overlap, which implies that these statements can only be done with the necessary restraints. The fact that no changes were observed for BMI could be due to the relatively small changes in fat%, hip and waist circumference: a 1-point decrease in BMI would require a weight loss of approximately 3 kg. The bioimpedance leg-to-leg method has been recommended as a practical tool that is accurate for clinical monitoring of fat% changes over time during weight management in older adults [44]. Xie et al. previously showed in postmenopausal women, a CV within days of 1.1% and a CV between days of 2.1% [71]. The changes in fat% observed in our study are 0.6/31.5=1.9% for the GA group versus 1.1/32.8 = 3.4% for the PA group. When we consider the CVs, we cannot be sure whether our results are due to measurement error or actual changes in fat%, although the beneficial effects seen in the PA group are in line with reduced waist and hip circumferences in this group.

There is a limited number of studies that previously investigated effects of lifestyle counselling on body composition and physical function outcomes in older adults [72, 73]. Harrigan et al. observed significant larger declines in hip circumference, waist circumference and fat percentage among participants receiving personal advice during a period of 6 months as compared to participants receiving usual care [72]. Santanasto et al. evaluated physical function scores among older adults receiving either a physical activity intervention or a general health education intervention on a weekly basis. In both study groups physical performance improved after 6 months, however the effects were stronger in the intervention group [73]. This is in line with our results as both PA and GA resulted in improved SPPB scores at the end of the study period. It has been suggested that among overweight or obese older adults, modest weight loss improves physical function, most likely through a decline in fat mass [74, 75].

Finally, while self-perceived vitality, specifically motivation and resilience (Vita-16), shows an indication for improvement over time for the PA group, self-perceived health did not improve. It could be that the study duration was too short after all to detect changes in self-perceived overall health, while changes in specific areas of vitality are potentially easier to detect over a shorter time frame. Motivation as measured with the Vita-16 reflects ´an individual's motivation to set goals in life and try to achieve these goals' [46]. as people in the PA group were actively involved in setting lifestyle goals and behavior change, this may have led to the increase in motivation. Resilience reflects an individual's ability to cope with the daily problems and challenges of life. The PA did provide participants concrete support

and tips in improving their lifestyle, but it is difficult to say what exactly caused the increase in resilience scores.

Remarkably, mental health scores as part of the SF-12 slightly increased within the GA group, while (both the generic and personalized) advice was not aimed at improving mental health. Improvements in mental health because of lifestyle change are not plausible after only nine weeks and the observed increase does not seem to be clinically relevant, as is also indicated by the absolute scores on mental health, which are not different between the two groups.

4.4. LIMITATIONS

Some limitations of this study must be considered. Firstly, multiple levels of personalization (genotype, phenotype, dietary intake, personality, preferences) are used. Therefore, it is not possible to conclude what aspect of the personalized advice was most effective. Previous studies demonstrated beneficial effects of personalized nutrition advice [19, 31], but it remains unclear whether personalization of advice based on genotype or phenotype has additional value compared to personalization based on dietary intake alone [20, 76]. Although personalization of advice based on phenotype or genotype may not have an added value with respect to compliance, there can still be an added value with respect to improving specific health outcomes in an individual. It would be interesting to compare a study group receiving PA with a group which receives help in implementing the general guidelines for healthy nutrition and physical activity. Then it will become evident whether further personalization on phenotype, genotype or eating habits has added benefit.

Secondly, and because of the explorative nature of the study, the sample size was not based on the statistical power needed for interaction effects. This could be an explanation for the relatively small (interaction) effects. Furthermore, the study population already relatively active, despite the high level of sedentary behavior, and had a generally healthy food pattern at baseline. In future studies, current activity patterns and dietary intake could be used as inclusion/exclusion criteria to ensure that there is more room for improvement.

Thirdly, participants in the study were instructed to use the device MijnEetmeter (Netherlands Nutrition Centre) for monitoring dietary intake. Besides tracking dietary intake, this device can also provide feedback on intake of calories, macronutrients, and some micronutrients. This implies that also the GA group received some feedback through MijnEetmeter, which may have interfered with our results. However, the feedback given by MijnEetmeter was based on dietary intake only, and focused on generic guidelines for calories, macronutrient intake (fat, saturated fat, protein, carbs, fiber) and salt. Next to the MijnEetmeter feedback, the PA group was provided a web portal that showed to which extent a participant reached the guidelines for different dietary categories with orange, red and green icons. This allowed this group to select those advice categories where there is most room for improvement for them personally. The GA group did not have such an opportunity.

Fourthly, the frequency of personalized feedback and advice in our study was fixed, however it can be assumed that the optimal frequency of personalized advice and reminders to the advice varies between individuals. To further optimize personalization of lifestyle advice, the relation between frequency of exposure and compliance should be further studied. Furthermore, we used personal health data as well as personal preferences to make the generic (population-based) recommendations more personal. Up to now, evidence-based knowledge on subgroups/strata of people is too limited to be used for personalized advice, however this will change in the coming years.

Finally, the duration of the study was relatively short. Based on previous studies, a period of nine weeks seemed sufficient to evaluate the initiation of behavior change [34] as well as of small physical health changes [35-39], however whether this behavior change persists and whether health effects are maintained should be further evaluated on the longer term. Despite these limitations we were able to show that personalized advice results in additional health effects compared to generic advice, therefore demonstrating that personalized advice has a strong potential for improving the wellbeing of older adults.

5. CONCLUSION

In the present explorative study, we showed that personalized advice may evoke health benefits in a population of seniors as compared to generic advice.

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A NOVEL PERSONALIZED SYSTEMS NUTRITION PROGRAM IMPROVES DIETARY PATTERNS, LIFESTYLE BEHAVIORS AND HEALTH-RELATED OUTCOMES: RESULTS FROM THE HABIT STUDY

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ABSTRACT

Personalized nutrition may be more effective in changing lifestyle behaviors compared to population-based guidelines. This single-arm exploratory study evaluated the impact of a 10-week personalized systems nutrition (PSN) program on lifestyle behavior and health outcomes. Healthy men and women (n = 82) completed the trial. Individuals were grouped into seven diet types, for which phenotypic, genotypic, and behavioral data were used to generate personalized recommendations. Behavior change guidance was also provided. The intervention reduced the intake of calories (−256.2 kcal; $p < 0.0001$), carbohydrates (−22.1 g; $p < 0.0039$), sugar (−13.0 g; $p < 0.0001$), total fat (−17.3 g; $p < 0.0001$), saturated fat (−5.9 g; $p = 0.0003$) and PUFA (−2.5 g; $p = 0.0065$). Additionally, BMI (−0.6 kg/m2; $p < 0.0001$), body fat (−1.2%; $p = 0.0192$) and hip circumference (−5.8 cm; $p < 0.0001$) were decreased after the intervention. In the subgroup with the lowest phenotypic flexibility, a measure of the body's ability to adapt to environmental stressors, LDL (−0.44 mmol/L; $p = 0.002$) and total cholesterol (−0.49 mmol/L; $p < 0.0001$) were reduced after the intervention. This study shows that a PSN program in a workforce improves lifestyle habits and reduces body weight, BMI, and other health-related outcomes. Health improvement was most pronounced in the compromised phenotypic flexibility subgroup, which indicates that a PSN program may be effective in targeting behavior change in health-compromised target groups.

1. INTRODUCTION

Public health dietary recommendations are designed to help most of the population avoid chronic disease. Personalization of these recommendations is limited to gender and age [1]. However, people also differ in genotype, phenotype, behavior, personality, and socio-psychological environment. Due to these differences, personal variation in response to dietary recommendations is likely. Indeed, research has shown that responses to nutritional interventions depend on differences in both genotype and phenotype [2–4]. Tailoring advice based on individual data also increases the perceived relevance of this advice [5]. Additionally, awareness of potential health problems leads to more favorable attitudes toward personalized nutrition [6,7]. Workforce wellness programs appear to be more effective if the content is tailored to participants' needs [8]. Thus, personalized nutrition approaches may be more effective in changing dietary and other lifestyle behaviors, ultimately improving health outcomes, as compared to guidelines derived for most of the population [9–12].

Personalized nutrition has been defined as "the use of individual-specific information, founded in evidence-based science, to promote dietary behavior change that may result in measurable health benefits" [13]. The effectiveness of personalized nutrition programs can be enhanced by using an integrated systems-based approach [14]. A four-step cycle of personalized nutrition was designed to improve and sustain health and function by combining objective health data and behavior change to meet individual needs and goals [13]. This cycle starts with collecting individual-specific information, which may range from an individual's current lifestyle and personal preferences to phenotype and genotype. In general, the level of personalization is dependent on the robustness and extensiveness of the available data [15]. The second step in the cycle is to translate individual data into evidence-based dietary recommendations. This requires the identification of food-health relationships using scientific knowledge and/or algorithms that can link individual data to dietary advice. Furthermore, it requires integration with a person's needs, context and preferences to promote understanding, adherence, and sustained behavior change [16,17].

The third component of the personalized nutrition cycle is to further promote dietary behavior change through the application of behavior change techniques, such as goal setting, self-monitoring, and positive feedback, which have been proven to be effective in increasing the likelihood of behavior change [18–21]. It has been shown previously that combining multiple approaches unique to the individual, including face-to-face contact, increases effectiveness [22–26]. Personalized behavior change support should also consider readiness and motivation to change [17]. Regarding goal setting, intrinsic motivation to achieve the goal and freedom in choosing goals are important determinants for success, both in the short and long term [27–29].

The fourth component of the personalized nutrition cycle measures the success of the advice and behavior change support; quantifiable improvements in health are essential. As

personalized nutrition approaches strive to become more individualized and holistic, measuring the effects of such interventions demands an outcome measure that considers multiple aspects of health. A holistic definition of health has been defined by Huber et al. as "the ability to adapt or cope with ever changing environmental conditions" [30,31]. The ability of the metabolic system to recognize an environmental challenge, respond, and return to homeostasis is referred to as phenotypic flexibility [32]. An unhealthy lifestyle is known to impair phenotypic flexibility and may negatively affect health [32]. For example, impaired phenotypic flexibility has been reported in overweight participants who have a reduced ability to metabolize stored lipids for energy synthesis and adapt more slowly to excess dietary fat intake, compared with lean participants [33]. Assessment of phenotypic flexibility can be used as a measure of metabolic health status to inform nutritional interventions [34–36]. The assessment of phenotypic flexibility requires the perturbation of homeostasis and subsequent evaluation of nutrition-related biomarkers. A nutrition challenge (i.e., tolerance tests) with a combination of fat, carbohydrates and protein has been successfully used to disturb homeostasis [33,34]. Drawing conclusions on the metabolic health status of an individual based on single biomarkers is challenging as it may provide an incomplete picture; thus, an aggregate marker could be calculated by integrating multiple metabolic markers into a composite score [37,38].

The objective of the current study was to determine the impact of an integrated personalized systems nutrition (PSN) program in a workforce. The PSN program included personalized dietary advice based on individual phenotype (challenge test response), genotype, and anthropometric data in combination with participant-generated data on diet, physical activity, goals, and preferences. The personalized dietary advice was provided via recipes and macro- and micronutrient recommendations, but also in the form of ready-made meals (breakfast and lunches). The PSN program included behavior guidance through individual coaching and motivational interviewing and behavior change promotion through goal setting, positive feedback, and self-monitoring. The effect of this 10-week PSN program on lifestyle behavior change, including dietary intake, activity, and sleep, was evaluated. Furthermore, the effect of this program on health outcomes, including individual markers and an aggregate score for metabolic health status (i.e., health space model) was also evaluated [39,40]

2. MATERIALS AND METHODS

2.1. Study Design

This was a single-arm, multi-phase, open-label exploratory trial that consisted of four 10-week periods preceded by a screening session (week −2). Each of the periods had a mid- and end-point visit: (i) baseline (week 0) and run-in (week 0–10), (ii) intervention phase 1: personalized coaching/advice and meals (week 10 to 20), (iii) intervention phase 2: personalized coaching/advice (week 20 to 30), (iv) follow-up (week 30 to 40, endpoint visit

only). The focus of this manuscript is on the methods and main results from data collected at baseline, during run-in and in phase 1 of the study, i.e., through week 20 **(**Figure 1). Due to a higher-than-expected dropout from phase 2, these data were excluded from the analysis. The study was conducted in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki [41], and the United States 21 Code of Federal Regulations. An institutional review board (Hummingbird IRB, Needham, MA, USA) approved the protocol before initiation of the study, and participants provided written informed consent before implementation of any study-specific procedures. This study was registered at clinicaltrials.gov as NCT03424395, which includes details of the study design and outcomes assessed.

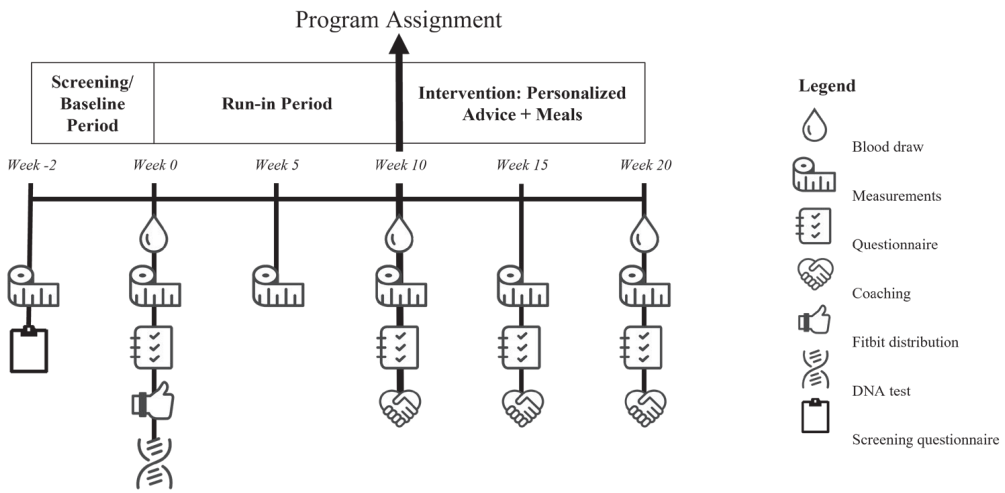

Figure 1*. Study design overview. The screening visit, run-in period and 10-week intervention (personalized advice and meals; phase 1) of a single-arm, multi-phase study. Screening consisted of anthropometric measurements and a screening questionnaire. After screening, participants had mid- and end-point visits/contacts during the run-in and intervention period. Participants completed an at-home challenge test and sample collection (weeks 0, 10 and 20; including DNA at week 0 only), anthropometric and body composition assessments (all weeks), electronic questionnaires (all weeks except 5), coaching (weeks 10, 15 and 20), and were distributed an activity tracker (Fitbit; week 0).*

2.2. Participants

Generally healthy men and women, 30 to 65 years of age, with body mass index (BMI) 18.5 to 39.9 kg/m^2 were recruited from a workforce (Campbell Soup Company, Camden, NJ, USA). Eligibility was assessed via a screening questionnaire (week 2). Eligible participants were those who met the inclusion criteria, were willing to follow all study procedures and who had access to an internet-ready device and a functioning personal email address. Participants were deemed ineligible based on the following exclusion criteria: a history or presence of diagnosed conditions that could interfere with study outcomes, uncontrolled hypertension, a current or recent history of nicotine or heavy alcohol use (>14 drinks per

week), current or recent use of lipid altering medications, allergy or sensitivity to the study foods provided or very specific dietary habits (e.g., vegan, very low carbohydrate), or a recent history of body weight change >10%. A complete description of all inclusion and exclusion criteria can be found on clinicaltrials.gov (NCT03424395).

2.3. Study Procedures Overview

At each visit, anthropometrics (height (first visit only), weight, fat mass, waist and hip circumference) [42] and blood pressure were assessed according to standard operating procedures by the study coordinator.

Validated questionnaires were administered electronically (REDCap Cloud, version 1.3, Encinitas, CA, USA) in weeks 0 (baseline), 10, 15 and 20. Additionally, participants were provided with an activity tracker at baseline (Charge 2, Fitbit, San Francisco, CA, USA) and were asked to wear the device for the remainder of the study.

In weeks 0, 10 and 20, participants were provided with an at-home kit including all necessities for challenge testing and dried blood spot (DBS) and DNA (week 0 only) sample collections. Prior to testing at baseline, participants were provided with private access to a digital platform which included video instructions and an on-boarding form for logging age, body weight and height, hypertension status (yes or no), waist circumference and physical activity history. Data from this form was used along with clinical and DNA results to generate personalized recommendations.

Personalized recommendations were provided to participants through a digital platform on week 10. Additionally, breakfast and lunch meals were provided and tailored to their macronutrient recommendations, five days a week for nine weeks, starting at week 10. Meal diaries were collected weekly to assess compliance. Video and phone coaching sessions were scheduled with participants in weeks 10, 15 and 20. Adverse events were evaluated at the beginning of each visit, except at screening.

2.4. At-Home Sample Collection and Challenge Test

Participants were instructed to avoid vigorous physical activity and fast for 10 to 14 h (water only) prior to completing the at-home kit. Sample collection began with buccal cell collection by cheek swab (week 0 only for DNA isolation) followed by fasting capillary blood (0 min). Challenge beverages were then consumed within a 5-min period and capillary blood collected at 30- and 120-min post-beverage consumption. All capillary blood was collected on DBS cards (Advance DX100, Advance DX, Inc., Chicago, IL, USA). Participants placed their DBS cards and cheek swabs in packets and brought them to the study office where they were logged and shipped for analysis (Aegis Sciences Corporation Nashville, TN, USA).

A nutrient dense mixed-meal beverage was used for challenge testing, which has been previously shown to effectively perturb metabolic homeostasis [43]. The challenge beverage

(414 mL; Jasper Products, Joplin, MO, USA) consisted of 60.1% (*w*/*w*) water, 13.6% (*w*/*w*) palm oil, 18.9% (*w*/*w*) dextrose, 5.3% (*w*/*w*) milk protein isolate, and <1.5% each of vanilla, cassia flavor, trisodium citrate, canola lecithin, and gellan gum. This resulted in a beverage of 3950 kJ/950 kcal with a macronutrient composition of ~64 g fat, 22 g protein and 88 g carbohydrate.

2.5. Personalized Systems Nutrition Program

Decision trees and algorithms were used to generate personalized dietary recommendations using individual on-boarding data (including self-reported body weight, waist circumference and blood pressure), clinical measures (including measures before and after a mixed-meal challenge test) and single nucleotide polymorphism (SNP) variants (Table 1) according to the proposed guidelines to evaluate scientific validity and evidence for genotype based dietary advice [44]. SNPs indicated in bold (Table 1) drove personalized dietary recommendations if the risk-variants of these SNPs coincided with an unhealthy phenotype. All other SNPs were only used to help provide additional context and supporting recommendations (Supplementary Table S1). Individuals were grouped into seven possible personalized diet types (PDTs) that differed in terms of phenotypic flexibility (A = highest possible flexibility to G = lowest flexibility). Personalized advice for these PDTs differed in terms of macronutrient profiles that met the USDA Dietary Guidelines for Americans [1] and/or Acceptable Macronutrient Distribution Ranges [45] (Table 2). PDTs were determined using onboarding data and clinical measures. SNPs did not independently determine diet type. If a risk variant for FTO rs9939609 coincided with a high waist circumference, this led to a high protein and low fat and carb PDT [46–48]. Energy intake advice was determined based on total energy expenditure. The basal metabolic rate was calculated using the Mifflin St. Jeor equation [49], which was then multiplied by the daily physical activity level (PAL) score. The total daily PAL was calculated as the sum of the daily pattern PAL score based on a categorization by Hall et. al. and PAL scores for sport and leisure activities [50,51]. Micronutrient recommendations were determined using onboarding, anthropometric and clinical measures and further supported by SNP data if physiological pathways were known. For instance, it has been shown that in hypertensive people with the MTHFR rs1801133 risk variant riboflavin supplementation may contribute to blood pressure lowering [52,53]. Finally, SNP-based narratives were provided for a few food-related sensitivities, physical activity, and vitamin D, which describe the linkages between the SNP and certain recommendations or health outcomes, but do not imply causality (Table S1).

In addition to the seven PDTs that guide macronutrient recommendations, the algorithms generated micronutrient and calorie recommendations. Micronutrient recommendations were personalized by age and gender (per U.S. RDAs), dietary intake, clinical measures, and SNP data [54,55].

Table 1. *Biological factors and cut-off values used to generate personalized recommendations [1].*

Advice Category	Personalized Advice	Personalization Factor [2]	Classification	Personalization Based on SNP
Energy intake advice	Caloric intake	body weight, height, age, gender, physical activity	Mifflin St. Jeor equation: BMR (kcal/day) = 10 × weight (kg) + 6.25 × height (cm) − 5 × age (y) + a_1 (kcal/day), a_1 = +5 for males and −161 for females. Total energy expenditure = BMR × daily PAL Total PAL = PAL daily pattern + PAL sport/leisure$_1$ + … + PAL sport/leisure$_n$	-
Personalized Diet Types & SNP-based macronutrient advice	Protein intake	glucose tolerance, disposition index [3], blood-pressure	normal = normal, glucose intolerance = IFG, IGT, IFG/IGT or T2D low disposition index (<1.5), normal disposition index (>1.5) optimal (SBP <120 and DBP <80 mmHg), elevated (SBP ≥120 or DBP ≥80 mmHg)	**FTO rs9939609 [5]**
	Carbohydrate intake	waist circumference, 2-h glucose	normal (M ≤ 40-inch, F ≤ 35 in), elevated (M > 40-in, F > 35 in) normal (<7.77 mmol/L; <140 mg/dl); elevated (≥7.77 mmol/L; ≥140 mg/dl)	**FTO rs9939609 [5]** ADAMTS9 rs4607103 GCKR rs780094
	Fat intake	waist circumference, blood pressure, LDL cholesterol	normal (M ≤ 40 in, F ≤ 35 in), elevated (M > 40 in, F > 35 in) optimal (SBP < 120 and DBP < 80 mmHg), elevated (SBP ≥ 120 or DBP ≥ 80 mmHg) normal (≤3.36 mmol/L; ≤130 mg/dl); elevated (>3.36 mmol/L; >130 mg/dl)	**FTO rs9939609 [5]** FTO rs1121980 TCF7L2 rs7903146 FADS1 rs174546 FADS1 rs174548 IGF2BP2 rs4402960 PPARG rs1801282
Micronutrient advice	Fiber intake	fasting glucose, 2-h glucose, LDL cholesterol, blood pressure, waist circumference	normal (<5.55 mmol/L; <100 mg/dl); elevated (≥5.55 mmol/L; ≥100 mg/dl) normal (<7.77 mmol/L; <140 mg/dl); elevated (≥7.77 mmol/L; ≥140 mg/dl) optimal (<2.59 mmol/L; <100 mg/dl); increased (≥2.59 mmol/L; ≥100 mg/dl) optimal (SBP < 120 and DBP < 80 mmHg), elevated (SBP ≥ 120 or DBP ≥ 80 mmHg) normal (M ≤ 40 in, F ≤ 35 in), elevated (M > 40 in, F > 35 in)	ADAMTS9 rs4607103 TCF7L2 rs7903146
	MUFA intake	disposition index [3] LDL cholesterol, blood pressure,	low disposition index (<1.5), normal disposition index (>1.5) normal (≤3.36 mmol/L; ≤130 mg/dl); elevated (>3.36 mmol/L; >130 mg/dl) optimal (SBP <120 and DBP <80 mmHg), elevated (SBP ≥120 or DBP ≥80 mmHg)	-

		fasting TG, postprandial TG [4],	normal (≤1.7 mmol/L; ≤150 mg/dl); elevated (>1.7 mmol/L; >150 mg/dl) normal (≤2.5 mmol/L); elevated (>2.5 mmol/L)	
	Omega-3 intake	blood pressure, fasting TG, postprandial TG [4], omega-3 index	optimal (SBP <120 and DBP <80 mmHg), elevated (SBP ≥120 or DBP ≥80 mmHg) normal (≤1.7 mmol/L; ≤150 mg/dl); elevated (>1.7 mmol/L; >150 mg/dl) normal (≤2.5 mmol/L); elevated (>2.5 mmol/L) optimal (>8 %); intermediate or low (≤8 %)	**FADS1 rs174546** [5] **FADS1 rs174548** [5]
	Phytosterols	LDL cholesterol	optimal (<2.59 mmol/L); increased (≥2.59-≤3.36 mmol/L); elevated (>3.36 mmol/L)	-
	Vitamin C intake	blood pressure, age, gender	optimal (SBP <120 and DBP <80 mmHg), elevated (SBP ≥120 or DBP ≥80 mmHg)	-
	Vitamin B2 intake	blood pressure, age, gender	optimal (SBP <120 and DBP <80 mmHg), elevated (SBP ≥120 or DBP ≥80 mmHg)	**MTHFR rs1801133** [5]
SNP-based narratives	Physical activity	-		ACTN3 rs1815739 FTO rs1121980
	Vitamin D	-		GC rs7041
		-		GC rs4588
		-		GC rs2282679
	Lactose intolerance	-		MCM6 rs182549
		-		MCM6 rs4988235
	Caffeine sensitivity	-		CYP1A2 rs762551
	Salt sensitivity	-		AGT rs5051
		-		AGT rs699

Abbreviations: BMR, basal metabolic rate; BW, body weight; DBP, diastolic blood pressure; F, females; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low density lipoprotein; M, Males; PAL, physical activity level; SBP, systolic blood pressure SNP, single nucleotide polymorphism; T2D, type 2 diabetes; TG, triglycerides. [1] This table is a simplified representation of the algorithms used for personalized advice; the actual algorithms are more complex and contain interdependencies; only a few micronutrient examples are included for illustration. Macro- and micronutrient recommendations were used to drive personalized recipes and meals. Complete algorithms and decision trees can be requested from the authors. [2] Personalization factors are variables that are used to drive personalized recommendations; these include demographics, anthropometrics, and blood biomarkers. [3] Disposition index is calculated from glucose and insulin response curves after the challenge beverage consumption.[4] Postprandial markers were measured at 30 and 120 min after challenge beverage consumption. [5] SNPs indicated in bold drove personalized dietary recommendations if the risk-variants of these SNPs coincided with an unhealthy phenotype; all other SNPs were only used to help provide additional context and supporting recommendations.

Finally, participants were provided with personalized recipes and meals according to their macro- and micronutrient recommendations [56]. Participants had access to a digital platform which included their personalized recommendations, test results and narratives explaining the participant's clinical, genotypic, and anthropometric data. Additional information on the decision trees and algorithms that were used can be provided upon request.

Table 2. *Macronutrient ranges and target for dietary programs for the personalized diet types (PDTs).*

	Carbohydrates	**Fat**	**Protein**
PDT	**% of Total Energy (Target %)**		
A	45–65 (50)	20–40 (30)	10–22 (20)
B	45–65 (60)	20–30 (20)	10–22 (20)
C	35–50 (45)	20–40 (40)	10–22 (15)
D	45–65 (45)	20–40 (25)	18–35 (30)
E	45–65 (45)	20–30 (20)	18–35 (35)
F	35–50 (35)	20–40 (30)	18–35 (35)
G	35–50 (40)	20–30 (25)	18–35 (35)

Coaching by a registered dietitian nutritionist (RDN) occurred three times for phase 1 (week 10 to 20) (Figure 1). RDNs were trained on coaching techniques as well as the algorithms behind the PSN program prior to the start of phase 1. Coaching sessions were provided by two RDNs who jointly developed the format of the sessions based on behavior science and held, at minimum, bi-weekly conference calls to review content for participants' sessions. During the first coaching session (week 10), which was a video conference, the RDN explained their clinical results to each participant and how they were linked to their personalized dietary recommendations. Additionally, readiness to change and self-efficacy were explored [57,58]. After the first coaching session, participants were instructed to set personal goals for at least one goal area (modifying eating behavior, exercise, sleep, general balance, and mindfulness) using SMART (specific, measurable, attainable, realistic, time-based) goal setting criteria [59]. To provide participants with a foundation for change, they were shown graphics and data during their session comparing their present reported dietary macro- and micronutrient intakes to their personalized program recommendations. Participants were provided the graphics and data electronically after the session for reference. Additionally, they were provided with food recommendations and considerations to help them achieve their program plan. During the second coaching session (week 11), delivered by phone, personalized behavior change SMART goals using the SMART criteria were reviewed and finalized. During the third coaching session (week 15) participants could touch base on goals or other issues related to their personalized program. Participants where shown their most recent food intake data compared to the personalized recommendations. Individual's chosen goals were reviewed to assess their progress and adjust behavior change as needed. This was followed by an electronically delivered report recapping the session.

Coaches used motivational interviewing strategies and techniques to facilitate behavior change at all sessions and contacts [57,58]. In addition to coaching, throughout phase 1, participants received information on how to follow their personalized diet via email and on their digital platform. This information included guidance on meals and snacks, eating out, and recipes for their PDT.

2.6. Study Meals and Compliance

Participants received tailored breakfast and lunch five days a week for nine weeks, beginning at week 10. All meals were prepared on-site (Sodexo Food Services, Gaithersburg, MD, USA) according to macronutrient distributions per assigned PDT (Table 1). When possible, food preferences were accommodated. Participants were provided with meal diaries weekly and asked to record how much of each meal they consumed. Responses were scored as follows: 'I did not eat' (0), '≤50%' (0.5), or' ≥50%' (1) and compliance was calculated as the percentage of meals consumed based on the number of meals provided.

2.7. Dietary Intake

Participants recorded all food and beverage intake consumed over three days (two weekdays and one weekend day) using a standard dietary record methodology prior to all visits except for the screening and week 5 visits [60]. At randomization, participants were instructed on how to collect dietary recalls, and shown household measuring cups, spoons, and a ruler, and instructed on how to obtain portion sizes on labels. The records were reviewed by an RDN who followed up by email if clarification was required. Records were analyzed using Food Processor Nutrition Analysis Software (version 11.6, ESHA, Salem, OR, USA) and nutrient intake and calories were averaged over the three days and used for statistical analyses.

2.8. Anthropometrics and Vitals

At each visit, anthropometrics (height (first visit only), weight, fat mass, waist and hip circumference) and blood pressure were assessed. Duplicate measures for body weight and fat were obtained using the BC-554 IRONMAN® Body Composition Monitor (Tanita, Arlington Heights, IL, USA) according to standard methodology as provided by the Tanita BC-554 scale. The Tanita BC-554 model has single frequency bioelectrical impedance analysis technology to assess changes in body fat and fat mass over time. The same Tanita scale was used for all participants throughout the entire duration of the study. Our protocol aimed to control for the effects of hydration state, body temperature, and time of day on measurements by educating participants on hydration status and conducting clinic visits at similar times. Waist and hip circumference were performed by the same study coordinator following the WHO standards [42]. Triplicate measures for blood pressure (Home™ 1500 Series Upper Arm Blood Pressure Monitor, Welch Allyn, Chicago, IL, USA) were taken according to standard operating procedures and the last two measurements were averaged.

2.9. Wellbeing and Lifestyle

Dietary behavior was assessed using the validated 34-item Adult Eating Behaviors Questionnaire (AEBQ) [61] which was administered electronically prior to visits at weeks 0 and 20. Quality of life (QOL) was assessed using the validated 26-item WHOQOL-BREF questionnaire [62], which was administered electronically at week 0, 10 and 20. Participants wore an activity tracker (Charge 2, Fitbit, San Francisco, CA, USA) from week 10 to 20 for assessment of daily activity (heart rate, number of steps) and sleep hours. Data was collected and stored using Fitabase (Small Steps Labs, San Diego, CA, USA) prior to analysis.

2.10. Laboratory Analyses

All laboratory analyses were performed by Aegis Sciences Corporation (Nashville, TN, USA). DNA was isolated from buccal samples and analyzed for quantity and quality using an RNaseP assay. A panel of SNPs, associated with dietary intake-related phenotypes, was investigated using qPCR on the TaqMan/Life Tech Platform™ (Thermo Fisher Scientific, Waltham, MA, USA). A 0.49-inch sample was punched from the serum eluded on the DBS cards. These cards are designed to separate the serum from cellular components of the whole blood and thus are subject to hematocrit bias/effect [63]. From this sample, serum glucose, triglycerides, total cholesterol, and HDL cholesterol were analyzed using enzymatic colorimetric tests on an Olympus 5400 (Olympus Corporation, Tokyo, Japan). LDL cholesterol was calculated using the Friedewald Equation [64]. A standard sandwich ELISA kit was used to assess C-peptide (Mercodia, Upsala, Sweden) using a Freedom EVO 150 platform fitted with a Columbus microplate washer and Sunrise microplate reader (Tecan, Mannedorf, Switzerland). All test results were normalized to total microprotein concentrations. Each normalized result was projected to a serum concentration using algorithms generated by Aegis Sciences Corporation.

2.11. Calculation of Insulin Sensitivity Indices

The glucose and C-peptide values derived from the challenge tests at all timepoints were used to calculate the following indices: simple Matsuda index and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) as measures of whole-body insulin resistance [65,66].

2.12. Statistical Analysis and Data Management

An evaluable sample of 100 participants was expected to provide 80% power assuming an alpha = 0.05, two-sided, and an effect size of 0.3 for health space score based on a previous nutritional intervention study [67].

A sample of 107 participants was enrolled to account for attrition and/or non-compliance (Figure 2). Tests of significance were performed at $\alpha = 0.01$ for questionnaires and Fitbit data and at $\alpha = 0.05$ for all remaining tests. The primary outcome variable was the health space score. All remaining outcomes were secondary. The analysis was completed on a per protocol

(PP) population, which was defined as follows: completing coaching session at week 10, and either completing a key questionnaire (WHOQOL-BREF) or vital signs and anthropometrics, with no major protocol deviations.

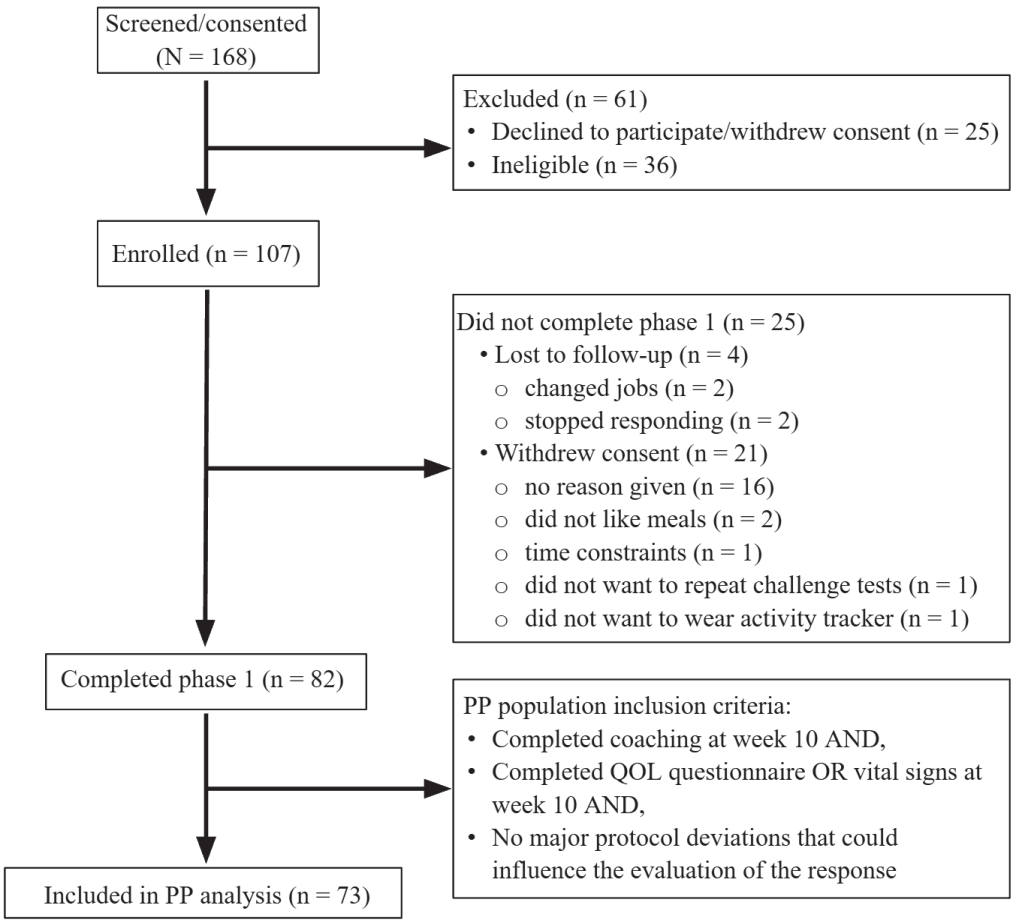

***Figure 2**. Study flow diagram. A total of 168 participants were screened/consented and healthy men and women were enrolled in the study (n = 107). A total of 82 participants completed phase 1 (personalized advice + meals intervention period; through week 20). Of the 25 participants that did not complete phase 1, four were lost to follow-up and 21 withdrew from the study. Data from 73 participants were included in the PP analysis. Abbreviations: PP, per protocol; QOL, quality of life.*

2.12.1. Health Space Model

The health space analysis is a multivariate supervised dimension reduction method that serves to summarize multiple variables into a single biologically meaningful score. Ridge regression was the applied method for the creation of health space models [68]. The model is a trained classifier that discriminates between two predefined reference groups [40]. During the training procedure, 10-fold cross validation was used to find the optimal shrinkage parameters for the model as well as to determine model quality using the misclassification

error. The data for each of the variables in the input dataset was centered on the mean and scaled by the standard deviation (Figure 3).

The reference groups were taken from previous research which aimed to create a health space representative of the normal range of health, using the phenotypic flexibility concept [40]. On the low end of the spectrum is the young and lean reference group (20 to 29 years of age, normal body fat percentage, which was <20% in male and <30% in female) while the high end of the spectrum is represented by the older group with a higher body fat percentage (60 to 70 years of age, body fat percentage ranging from normal to high, which was >20% in male and >30% in female) [40]. The number that is produced by providing this model with data from the study participants is termed the 'health space score'.

In summary, the health space score presented here aligns with the range of metabolic states within a normal healthy population. A higher score represents reduced phenotypic flexibility and a higher degree of similarity with older people with higher adiposity, while a low score suggests a greater degree of resilience and a higher degree of similarity with a young lean group.

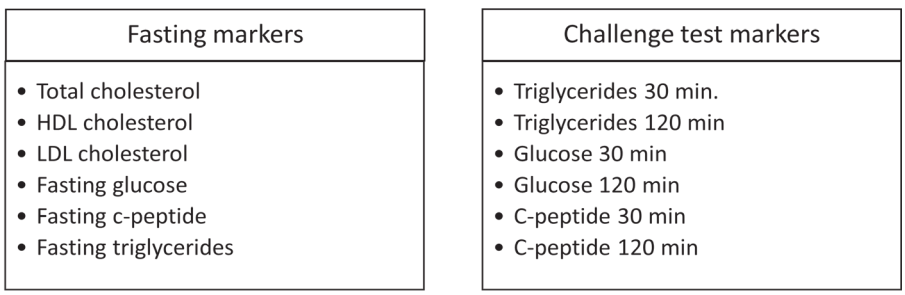

Figure 3. *Data used in the health space model. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. Postprandial markers were measured at 30 and 120 min after challenge beverage consumption.*

2.12.2. Wellbeing Questionnaires and Activity/Sleep Data Analysis

For the WHOQOL-BREF [62] and the AEBQ [61] the (sub)scales were calculated according to the official guidelines.

The Fitbit data provided information on the number of steps taken, resting heart rate and the hours of sleep. For the number of steps taken, the average steps per day over the phase preceding the measurement point was used. For resting heart rate and hours of sleep a similar approach was used.

The questionnaire and Fitbit data were evaluated using a linear mixed effect model where the intercept is dependent on the individual; this is akin to a repeated measurement model. Due to the nature of the data, PDT, gender and timepoint were used as explanatory variables.

When multiple time points were evaluated, time point was included as a covariate. The assumptions of linearity, normality and homoscedasticity were checked for each significant model. A 0.01 level was used to justify a claim of a statistically significant effect. Statistical analyses were completed using R software (version 3.5.1; The R Foundation, Vienna, Austria).

2.12.3. Linear Mixed Model Univariate Analysis

All remaining variables were assessed by univariate analysis using linear mixed models. For the univariate analysis, linear mixed models were used. All variables were LOG transformed before statistical analysis. A mixed model was used for statistical analysis. In this model, the focus was on visit and PDT including its interaction. Age, gender, and cohort were three covariates in the model. In this model age, gender, cohort, visit, PDT and PDT × visit were fixed factors. The participants within a cohort represented the random factor. If significant effects were observed, post-hoc tests were applied. To correct for multiple testing, a Tukey–Kramer multiple comparison correction was applied on the *p*-values of the post-hoc tests. Assumptions of normality and homoscedasticity were investigated by graphical representations on residuals produced by statistical models. If the model residual of any data point was larger than 3 × RMSE (root mean squared error) for a certain variable, the data point was considered as a statistical outlier for this variable and removed from the data set before creating a new model. For all statistical tests using the linear mixed model, a 0.05 level was used to justify a claim of a statistically significant effect. The tests conducted were two-sided. This analysis approach was used for all data except for the psychological questionnaire and Fitbit data. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1. Study Logistics and Baseline Characteristics

Between October 2017 and February 2018, 168 individuals were recruited and assessed for eligibility (Figure 2). Initially, 107 participants were enrolled in the study. A total of 82 participants completed the phase 1 intervention (week 10 to 20). The per protocol (PP) population included a total of 73 participants (Table 3).

Participants mainly selected modifying eating behavior as their primary goal (~56%) during the coaching sessions, followed by exercise (~33%) and mindfulness (~11%). None of the participants selected sleep or general balance as a primary goal.

***Table 3**. Descriptive statistics for the per protocol (PP) and subgroup populations (group A, group G) at inclusion (week 0).*

Variable	PP (*n* = 73)		Group A (*n* = 48)		Group G (*n* = 22)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Gender (*n*, men/women)	25/48		15/33		9/13	
Age (years) **	43.1	8.7	40.9	8.1	47.8	8.3
Anthropometrics and Vitals						
BMI (kg/m^2) ***	27.4	4.0	26.0	3.3	30.5	3.6
Body weight (kg) **	77.8	15.5	72.6	13.2	89.4	14.6
Body fat (%) ****	32.0	7.6	30.3	6.8	36.8	7.1
Muscle mass (kg)	50.1	10.7	48.3	9.9	53.7	11.8
Waist circumference (cm) ****	94.6	13.0	89.7	10.7	105.7	10.7
Hip circumference (cm) **	104.8	10.1	102.4	8.4	111.9	7.0
Systolic blood pressure (mmHg)	119.2	16.4	116.6	16.1	123.1	16.4
Diastolic blood pressure (mmHg)	73.7	8.7	72.2	8.0	75.6	8.6
Clinical Chemistry (fasting)						
C-peptide (nmol/L)	0.48	0.20	0.43	0.15	0.54	0.21
Glucose (mmol/L)	4.41	0.47	4.30	0.44	4.64	0.47
HDL (mmol/L)	1.52	0.40	1.60	0.43	1.39	0.27
LDL (mmol/L)	2.62	0.54	2.54	0.47	2.78	0.65
Total cholesterol (mmol/L)	4.68	0.66	4.66	0.62	4.70	0.75
Triglycerides (mmol/L)	1.15	0.57	1.11	0.61	1.25	0.51
Indices						
HOMA-IR	0.094	0.043	0.082	0.029	0.119	0.057
Matsuda index	212.0	82.4	230.8	77.5	176.2	79.0

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; *n*, number of observations PP, per protocol; SD, standard deviation. Statistically significant differences between group A and group G at baseline are noted (** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Within the PP population, two PDTs were mainly represented, which were group A (*n* = 48) and group G (*n* = 22); only three participants were classified into one of the other PDT categories (group B, E and F). For this reason, we restricted the discussion to diet type groups A and G only. As a result of the automated PSN algorithms, which assigned one of seven PDTs based on metabolic health status at baseline, groups A and G represent the most and least phenotypically flexible groups, respectively. Group G had a higher degree of adiposity and a higher age as compared to group A (Table 3). No differences in dietary patterns were

observed at baseline between the two PDTs. Both groups were 82% compliant with personalized meal intake.

3.2. Run-in Period Effects (Qualitative Control)

The run-in period (week 0 to 10), which was the same duration as the intervention period, provides an indication of behavior and health effects of being included in a clinical study (without being provided with the personalized nutrition program) and served as a qualitative control. In terms of dietary intake, total fat intake increased (+7.5 g; $p = 0.037$) from week 0 to 10 (Supplementary Table S2). This may be attributed to a higher intake of monounsaturated fatty acids (MUFA) (+4.3 g; $p = 0.003$) and polyunsaturated fatty acids (PUFA) (+2.5 g; $p = 0.003$). For group G only, there was a decrease in beta-carotene intake (−1031 mcg; $p = 0.007$) (results not shown). Additionally, some small but unfavorable health differences were found. Fasting and 2 h C-peptide (+0.11 nmol/L $p = 0.009$ resp. +0.25 nmol/L; $p = 0.003$) as well as 2 h glucose levels (+0.31 mmol/L; $p = 0.042$) were elevated after the run-in period. Consequently, HOMA-IR (+26.6%; $p = 0.001$) increased, and Matsuda index decreased (−15%; $p = 0.0004$), indicating an increased state of whole-body insulin resistance.

3.3. Intervention Effects

3.3.1. Dietary Intake

Many dietary intake changes were observed. For the PP population, intake of calories (−256.2 kcal; $p < 0.0001$), carbohydrates (−22.1 g; $p = 0.0039$), sugar (−13.0 g; $p < 0.0001$), total fat (−17.3 g; $p < 0.0001$), saturated fat (SFA) (−5.9 g; $p = 0.0003$) and PUFA (−2.5 g; $p = 0.0065$) were reduced during the intervention (week 10 to 20) (Table 4 and Table S2).

Energy intake from fat was significantly reduced and there was a small but significant increase in energy intake from fiber. When looking at differences between the PDT, percent calories from protein significantly increased in group G and not in group A, reflecting compliance with personalized dietary advice for these groups (Table 2 and Table 4).

For micronutrient intake, significant increases were seen during the intervention period for vitamin C (+33.6 mg; $p = 0.0002$), magnesium (+47.7 mg; $p = 0.0029$) and potassium (+327.4 mg; $p = 0.0328$) in the PP population. Finally, sodium levels were significantly reduced (−546.0 mg; $p = 0.0007$). When looking at subgroups, a significant increase in beta-carotene intake was seen in group G, but not group A.

3.3.2. Wellbeing and Lifestyle

For the PP population, the total steps per day increased, and the resting heart rate decreased during the intervention (Table 4 and Table S2). In terms of eating behavior, the only change observed was a higher satiety response after a meal in the PP population.

A significant positive correlation between the WHOQOL physical scale score at week 10 and the number of steps taken during intervention (correlation = 0.447; $p < 0.001$) was observed. Additionally, a positive correlation between the change in steps over time (change in steps from run-in period as compared to intervention period) and the WHOQOL health scale score at week 10 was observed (correlation = 0.39; $p< 0.01$).

3.3.3. Anthropometrics and Vitals

After the intervention period (week 10 to 20), during which participants received personalized dietary recommendations, coaching and personalized meals, several health improvements were observed for the PP population. While this was not designed to be a weight loss trial, BMI (−0.6 kg/m^2; $p < 0.0001$), body fat (−1.2%; $p = 0.0192$) and hip circumference (−5.8 cm; $p < 0.0001$) showed a significant decrease from week 10 to 20 for the PP population (Table S2), and body weight significantly decreased after the intervention in both group A and group G (Table 5, Figure 4).

3.3.4. Clinical Chemistry

For group G, significant reductions were observed in LDL cholesterol and total cholesterol during the intervention (week 10 to 20) (Table 5, Figure 4).

3.3.5. Health Space

A health space score was calculated where complete datasets were available ($n = 63$ at week 10 and $n = 49$ at week 20). Analysis of the health space showed that both biological age and BMI were positively correlated with health space scores (Figure 5). A higher health space score reflects lower metabolic health status. No differences in health space scores were observed between group A and group G ($p = 0.474$). Furthermore, no changes in health space scores due to the intervention were found for either the PP population ($p = 0.380$) or subgroups ($p = 0.113$).

Table 4. *Descriptive statistics of lifestyle factors during the intervention period (weeks 10 to 20).* [1]

	Week 10: Mean (SD)		**Week 20: Mean (SD)**		**Difference: Week 20–Week 10 (%)** [1]	
	A (*n* = 48)	**G (*n* = 22)**	**A (*n* = 48)**	**G (*n* = 22)**	**A (*n* = 48)**	**G (*n* = 22)**
Calories (kcal) ***	1877.1 (554.4)	1974.0 (520.0)	1681.5 (490.6)	1613.5 (324.5)	−10.40%	−18.30%
Carbohydrates (g) **	189.9 (64.9)	217.4 (83.1)	182.0 (58.3)	163.6 (43.5)	−4.20%	−24.70%
Carbohydrates (en%)	40.6 (7.2)	43.4 (5.4)	43 (6.6)	40.9 (8.5)	6%	−5.80%
Protein (g)	87.9 (24.8)	82.7 (16.2)	79.9 (24.6)	88.8 (27.6)	−9.10%	7.40%
Protein (en%)	19.1 (3.8)	17.3 (3.5)	19.9 (4.3)	22.0 (5.5)	4.10%	27.7% **
Fat (g) ****	80.2 (27.7)	82.6 (21.2)	65.0 (22.2)	62.4 (16.8)	−18.90%	−24.70%
Fat (en%) **	38.2 (5.4)	37.9 (5.8)	34.6 (6.2)	34.7 (5.0)	−9.50%	−8.50%
SFA (g) ***	25.8 (10.3)	25.2 (7.1)	20.6 (7.2)	18.8 (6.6)	−20.30%	−25.50%
SFA (en%)	12.3 (3.0)	11.7 (3.0)	11.0 (2.6)	10.4 (2.3)	−10.60%	−11.70%
PUFA (g) **	12.4 (5.9)	11.7 (5.5)	9.6 (4.7)	9.3 (4.3)	−22.60%	−20.50%
PUFA (en%)	6.0 (2.3)	5.4 (2.5)	5.2 (2.0)	5.1 (2.0)	−12.60%	−5.60%
MUFA (g)	22.0 (10.6)	20.4 (10.8)	17.8 (8.6)	17.0 (8.0)	−19.10%	−16.80%
MUFA (en%)	10.5 (3.5)	9.2 (3.6)	9.7 (3.4)	9.4 (3.3)	−8.50%	1.60%
Total sugar (g) ****	63.9 (33.5)	82.7 (40.5)	55.8 (30.2)	55.6 (23.9)	−12.70%	−32.70%
Total sugar (en%)	13.7 (5.7)	16.3 (5.1)	13.3 (5.4)	13.8 (5.4)	−3.90%	−15.70%
Total fiber (g) [2]	17.3 (5.6)	17.6 (8.0)	19.0 (6.1)	17.8 (5.9)	9.70%	1.60%
Total fiber (en%) [2] ****	1.9 (0.6)	1.8 (0.6)	2.4 (0.8)	2.2 (0.7)	25.50%	24.70%

Micronutrient intake [1]						
Sodium (mg) ***	2799.6 (895.5)	2795.3 (885.2)	2212.8 (892.3)	2371.7 (829.7)	−21%	−15.20%
Potassium (mg) *	1983.7 (781.0)	1777.7 (714.6)	2241.1 (716.4)	2233.8 (831.9)	13%	59.40%
Magnesium (mg) **	187.3 (66.7)	222.3 (150.5)	238.5 (82.5)	257.9 (78.2)	27.30%	15.90%
Vitamin C (mg) ***	74.4 (55.2)	72.3 (39.1)	106.1 (67.3)	111.8 (58.4)	42.60%	54.50%
Beta-carotene (mcg)	3074.0 (4330.5)	1534.2 (2740.1)	3415.7 (2518.0)	5970.8 (4316.1)	11.10%	289.2% ****
Physical activity [3]						
Resting heart rate (bpm) ****	63.4 (6.9)	66.0 (7.1)	62.4 (6.7)	63.6 (7.0)	−1.70%	−2.90%
Steps (*n*/day) ****	9319 (3073)	8558 (1856)	10234 (3206)	8957 (1865)	8.50%	6.50%
Sleep [3]						
Sleep (h/day)	7.3 (0.7)	6.9 (1.1)	7.1 (1.2)	7.0 (1.1)	−2.80%	1.40%

Abbreviations: bpm, beats per minute; en, energy; MUFA, monounsaturated fatty acid; *n*, number of observations; PP, per protocol; PUFA, polyunsaturated fatty acids; SD, standard deviation; SFA, saturated fatty acids. [1] Statistically significant differences are noted in the last two columns for changes in groups A or G, respectively, and in the first column for changes in the PP population (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$). [2] The 'TotalFiber_2016_p' variable was used as the time of analysis was considered a more reliable indicator of fiber intake than the 'post-2016 fiber' variable (Food Processor Nutrition Analysis Software, ESHA, Salem, OR, USA). The ESHA database is built based on food labels and restaurant labeling as well as the USDA database. The FDA change in fiber qualifications has not fully translated into the "post-2016 fiber" variable. [3] Physical activity and sleep differences were considered statistically significant at $p < 0.01$.

Table 5. *Descriptive statistics of anthropometrics, vitals, clinical chemistry, and indices values during the intervention period (weeks 10 to 20).*

Variable [1]	**Week 10: Mean (SD)**		**Week 20: Mean (SD)**		**Difference: Week 20-Week 10 (%) [1]**	
	A (*n* = 48)	**G (*n* = 22)**	**A (*n* = 48)**	**G (*n* = 22)**	**A (*n* = 48)**	**G (*n* = 22)**
Anthropometrics and Vitals						
BMI (kg/m^2) ****	26.0 (3.4)	30.7 (3.8)	25.7 (3.3)	29.9 (3.8)	−1.20%	−2.60%
Body weight (kg)	73.0 (13.4)	90.0 (15.0)	72.1 (13.3)	89.0 (15.4)	−1.2% **	−1.1% ****

Body fat (%) *	30.5 (7.1)	36.2 (6.0)	29.8 (6.9)	35.9 (6.7)	−2.30%	−0.90%
Muscle mass (kg)	48.3 (9.7)	54.2 (11.6)	48.1 (10.0)	54.4 (11.7)	−0.50%	0.40%
Waist circumference (cm)	89.5 (11.0)	104.5 (11.8)	89.0 (9.5)	104.3 (11.8)	−0.60%	−0.20%
Hip circumference (cm) ****	101.2 (8.4)	111.5 (7.3)	99.6 (8.4)	108.0 (7.8)	−1.60%	−3.10%
Systolic BP (mmHg)	118.0 (13.8)	122.8 (15.8)	114.7 (15.0)	119.2 (14.3)	−2.80%	−2.90%
Diastolic BP (mmHg)	73.8 (7.7)	76.5 (8.2)	70.9 (7.1)	74.8 (9.1)	−3.90%	−2.20%
Clinical Chemistry (fasting)						
C-peptide fasting (nmol/L)	0.54 (0.24)	0.68 (0.23)	0.47 (0.19)	0.66 (0.25)	−12.10%	−2.70%
C-peptide 2 h (nmol/L)	1.39 (0.69)	1.91 (0.73)	1.42 (0.79)	1.73 (0.69)	1.90%	−9.70%
Glucose fasting (mmol/L)	4.48 (0.47)	4.75 (0.41)	4.68 (0.51)	5.18 (0.49)	4.50%	9.00%
Glucose 2 h (mmol/L)	5.37 (0.83)	5.94 (0.87)	5.56 (0.72)	6.10 (0.63)	3.60%	2.70%
HDL cholesterol (mmol/L)	1.54 (0.39)	1.38 (0.40)	1.62 (0.40)	1.28 (0.36)	5.10%	−6.80%
LDL cholesterol (mmol/L)	2.67 (0.53)	2.88 (0.64)	2.44 (0.50)	2.44 (0.40)	−8.40%	−15.4% **
Total cholesterol (mmol/L)	4.70 (0.60)	4.96 (0.74)	4.61 (0.61)	4.46 (0.61)	−2%	−9.9% ****
Triglycerides (mmol/L)	1.16 (0.61)	1.58 (0.56)	1.32 (1.0)	1.64 (0.47)	13.20%	3.70%
Indices						
HOMA-IR	0.108 (0.050)	0.142 (0.046)	0.100 (0.045)	0.154 (0.062)	−7.40%	8.50%
Matsuda index	202.8 (89.2)	129.9 (40.6)	191.1 (66.9)	125.8 (45.7)	−5.80%	−3.20%

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; *n*, number of observations; PP = per protocol; SD, standard deviation; [1] Statistically significant differences are noted in the last two columns for changes in groups A or G respectively and in the first column for changes in the PP population (* $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$).

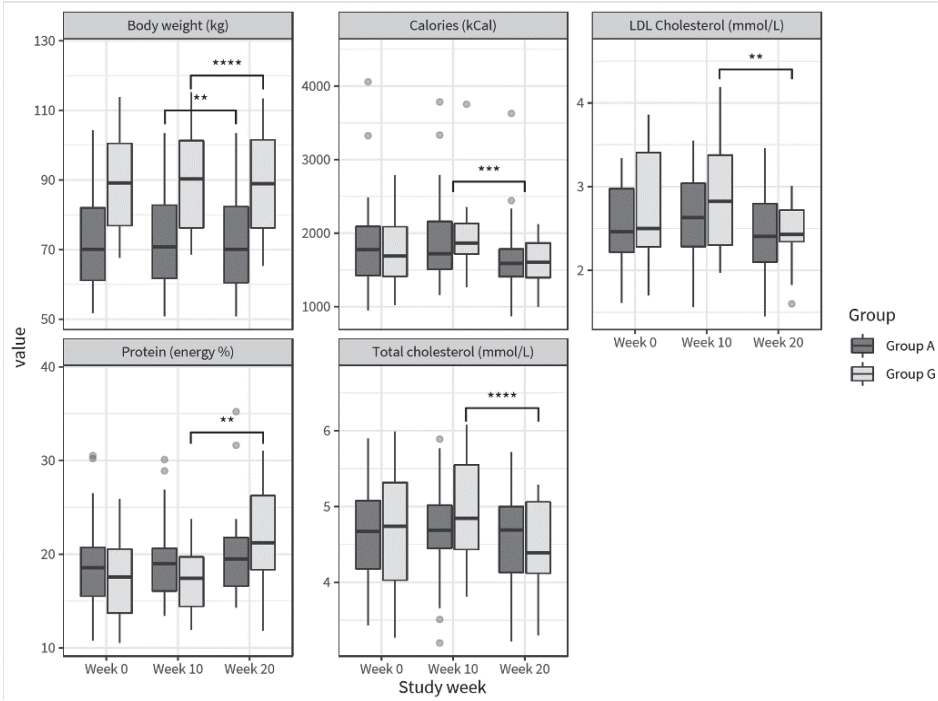

Figure 4. *Boxplots of body weight (kg), protein intake (energy %), calorie intake (kcal), LDL cholesterol (mmol/L) and total cholesterol (mmol/L), grouped according to personalized diet type; dark grey box plots represent group A (n = 48), and light grey box plots represent group G (n = 22). Subgroup specific statistically significant differences are noted (** p < 0.01; *** p < 0.001; **** p < 0.0001) over time, except for calories where a statistical difference for the PP population is indicated.*

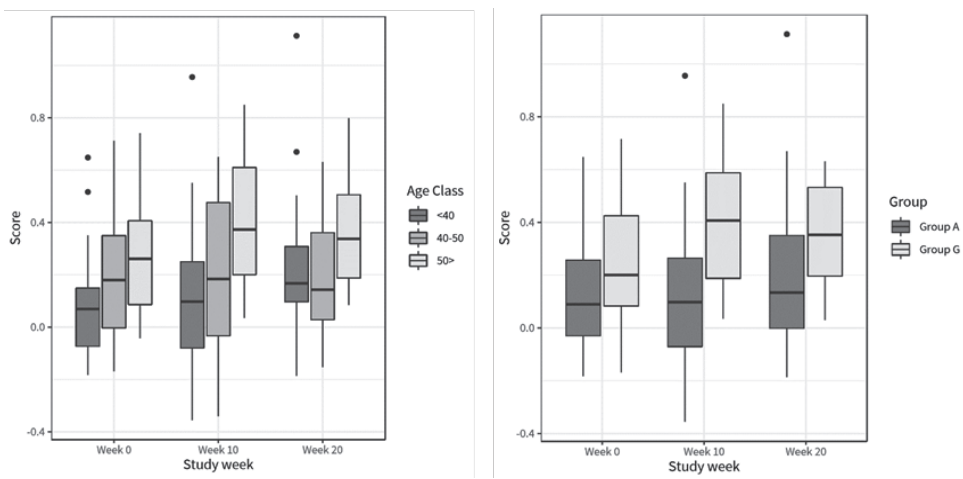

Figure 5*. Boxplots of health space scores for baseline (week 0, n = 73), end of run-in (week 10, n = 63) and end of intervention (week 20, n = 49), grouped according to age (left) and personalized diet type (right). A lower score on the health space is considered healthier.*

4. DISCUSSION

This study shows that a PSN program in a workforce improves dietary habits and physical activity and reduces body weight, BMI, and other health-related outcomes. These changes were most pronounced in group G, the subgroup with a compromised phenotypic flexibility at baseline.

While this study was not designed to promote weight loss, the PSN program resulted in an overall reduction in caloric intake, and an improvement in diet quality, as reflected by a decreased intake of total and saturated fat, sugar and sodium. Additionally, a decrease in absolute intake of PUFA was seen, but as there were no changes in energy percentage from PUFA, this is likely caused by the reduction in caloric intake. Overall, the reduction in total and saturated fat intake, sugar and sodium during the intervention period reflects an improved diet quality. This is further underscored by improvements in micronutrient intake, in terms of increased vitamin C, magnesium, potassium and beta-carotene intake, suggesting a higher intake of fruits and/or vegetables [69–71]. An increase in fruit and vegetable intake is in line with the personalized meals, recipes, and suggestions for both subgroups. Overall, the nutrient data suggests that after the personalized intervention, participants showed eating habits that are more aligned with population-based dietary recommendations. When looking at subgroups, the PSN program not only improved adherence with population-based dietary guidelines, but also better alignment with personal needs was achieved. For group G, different positive effects were seen with respect to dietary intake, consistent with their respective dietary recommendations. Protein (as a percentage of total energy) and beta-carotene intake increased during the intervention period in group G, but not in group A. The increase in protein intake can be directly related to the personalized advice of group G, as they were recommended to consume a diet high in protein and low in carbohydrates and fat. The increase in beta-carotene intake could be the result of a higher intake of fruits and vegetables. It should be noted that the personalized ready-made meals for group G were higher in protein and beta-carotene compared to the meals for group A. These results indicate that personalized nutrition programs may be effective in motivating people to consume a diet that meets individual needs while moving them closer to public health recommendations overall. As such, personalized nutrition programs seem to have added value as compared to general guidelines or one-size-fits-all approaches. Therefore, personalized offerings could be an interesting strategy in improving adherence with general dietary guidelines, by using general dietary guidelines as the basis for personalized nutrition and further finetuning these recommendations to individual needs and preferences.

Besides improvements in dietary intake behavior, the intervention resulted in increased physical activity in the PP population. Additionally, a small decrease in resting heart rate was apparent, which could indicate improved physical fitness [72–74]. However, it is unclear whether a small reduction in 1.3 bpm resting heart rate is clinically meaningful. The improvement in physical activity is an interesting finding, as the intervention consisted of

dietary advice only and participants did not receive any recommendations on their physical exercise. This increase in physical activity thus seems to be a beneficial side-effect of being involved in the PSN program.

The improvements in dietary intake and physical activity are supported by improvements in health parameters during the intervention, including body fat, BMI, body weight, hip circumference and total and LDL cholesterol. The reduction in body fat, BMI, body weight and hip circumference are relatively small and may not be clinically meaningful. A 3 to 5% of weight loss can be considered clinically meaningful, while in our study weight loss was ~1% [75]. However, this was achieved with a normal diet that did not focus on weight loss. These declines may become clinically meaningful if they persist with a continued healthy eating pattern. The reduction in BMI, body fat and hip circumference in the PP population during the intervention period can be explained by the reduced calorie intake and increased step count, suggesting a negative overall energy balance [76–78].

When looking at differences between the two PDTs, the degree of weight loss was more consistent for group G ($p < 0.0001$) as compared to group A ($p < 0.01$). At baseline, group G already had a significantly higher BMI as compared to group A, potentially leaving more room for improvement. However, body weight was not significantly different between groups. One could argue that the more consistent weight reduction in group G could be a result of higher protein intake, which has been shown to aide in weight loss [79–82], possibly because of improved satiety, appetite, and diet-induced thermogenesis [83,84]. This was also reflected in the increased satiety response during the intervention, although this change was seen for the PP population and was not specific for group G.

The decreased total and LDL cholesterol for group G may be partly explained by the reduced total and saturated fat intake during the intervention, as it has previously been shown that a higher saturated fat intake is correlated to higher total and LDL cholesterol levels [85–87]. However, the decrease in saturated fat intake during the intervention was similar for group A and G. Additionally, this decrease in total and LDL cholesterol in group G cannot be ascribed to baseline between-group differences and is likely a result of the PSN program. It has been proposed by the International Society of Nutrigenetics/Nutrigenomics (ISNN) that personalized advice should be more effective in preventing chronic disease than population-based dietary guidelines [88]. This study indeed suggests that personalized advice may be important to achieve desired health and functional outcomes. Additionally, the differential effects between subgroups indicate the added value of personalization. This suggests that personalized nutrition may enable changes in dietary intakes that have not occurred through public health recommendations. Previous research comparing DNA-based dietary guidelines with population-based dietary guidelines indeed showed greater changes in the intake of specific dietary components in the personalized group [89,90]. This could be explained by the fact that dietary guidelines only distinguish recommendations based on gender and age, whilst personalized nutrition can use more specific and detailed personal information in

generating relevant dietary advice. While more research is needed to see if these changes can be sustained over time, the results suggest that personalized approaches to health may be more effective than general guidelines and mass media campaigns for achieving dietary goals. In addition to providing a means to improve health, it also provides a means to work more closely with regulators. Moving from population-based programs to personalized recommendations and claims is new to many regulators. Personalized approaches can align to and support adherence to population-based guidance, which may help personalized programs gain greater acceptance [13,91].

Despite the differences in individual measures of health, no overall health effect could be observed using the health space score. Furthermore, there were no significant differences in health space scores between group A and G. This may be ascribed to the small number of participants with sufficient data for health space analysis (n = 46), whilst the power calculation indicated that data for 100 participants were required to detect a significant change. Additionally, the intervention period was only 10 weeks, which is relatively short to achieve significant changes in the total set of biomarkers. As there were substantial improvements in dietary intake and markers of health status, it could be expected that changes in health space may have been observed with a longer intervention. Furthermore, the largest subgroup in the study consisted of group A (n = 48), representing subjects who were most phenotypically flexible. For this PDT, there may have been less opportunity for health improvement based on the markers used, as opposed to the smaller group G (n = 22), which forms the least flexible PDT. Despite this limitation, we were still able to show an overall improvement in dietary behavior in our study as well as on single health outcomes.

Our findings are consistent with previous studies on personalized nutrition programs, which also show benefits of personalized advice as compared to a control group [9,92]. Previous reports have suggested that it is unclear whether personalization based on phenotype or genotype has additional value as compared to only using dietary intake for personalization [93,94]. A recent systematic review on the effect of incorporating genetic testing results into nutrition counseling on dietary intake concludes that disclosure of genetic information in carriers of high-risk gene variants may produce benefits, but results should be interpreted with caution due to the limited number of studies and large heterogeneity [95]. In the present study, phenotype and genotype, and not dietary intake data, were used to create PDTs. However, the included SNPs only played a minor role in the personalized advice, and thus probably had a limited effect on the study results. Our results mainly demonstrate that biological markers can be effectively used for personalization of advice leading to improvements in diet quality and health status. For example, we found improved total and LDL cholesterol and more consistent weight loss in the subgroup with a reduced health status. This beneficial effect might not have occurred if the personalized advice would have been based on dietary intake information only. A recent consensus report from the Academy of Nutrition and Dietetics also states that personalized nutrition requires a holistic approach that reflects lifestyle, preferences, health status and other domains of nutrition care [96,97].

It has been recognized previously that not only the information used for personalization of advice is of importance, but personal goals, barriers and preferences are also essential in the adoption of lifestyle changes [98]. The incorporation of these factors in our study, and thereby taking a holistic approach to personalized nutrition, may partially explain the intervention success. Surprisingly, an individual's perceived health and quality of life also seems to influence intervention success. In this study, a higher self-reported physical health score at baseline was associated with a higher number of steps after the intervention. Additionally, a higher perceived health was associated with a larger change in steps during the intervention period. This suggests an association between steps or physical activity and health satisfaction. It has been previously reported that a lower perceived physical and psychological health can form barriers for lifestyle behavior change [99,100]. In other words, people with a lower self-reported quality of life may experience more barriers for lifestyle behavior change, which may result in a lower effectiveness of lifestyle interventions. It has been shown that behavioral treatment strategies, including goal setting and motivational interviewing, improve adherence to lifestyle intervention programs [16,101]. The incorporation of such strategies in our personalized nutrition program may explain the high (82%) compliance rates with the personalized meals in this study. The results underscore the importance of providing both personalized dietary recommendations based on an individual's biological data as well as tailoring behavior advice to achieve better compliance.

Investigating the sustainability of intervention adherence and the beneficial effects of our PSN program over time would require long-term follow up of participants. However, it has been shown previously that challenge testing is a highly sensitive approach in detecting subtle changes in health [35,37], which could allow for fine-tuning the personalized advice to changes in health status over time. In the future, it could be interesting to consider an *n*-of-1 approach, which focuses on changes over time within an individual and could therefore help identifying differences in effectiveness of personalized programs between subjects and subgroups on a more detailed level.

4.1. Limitations

There were some limitations to this study that should be considered. First, by design, the distribution of participants over the subgroups could not be influenced, as the automated PSN algorithms assigned participants into one of seven PDTs after enrollment. Unfortunately, this resulted in an unequal distribution, with only two out of seven PDTs frequently occurring.

Second, self-measurements were used for generating the personalized dietary advice. During the onboarding process, participants self-measured their body weight, height, and waist circumference and reported on hypertension status (yes or no). When using waist circumference and blood pressure data as assessed by the study team during the baseline visit instead of the self-reported data for assigning the PDT, 22 participants in group A should have been classified as group E. Most misclassifications occurred because hypertension was not

reported by hypertensive participants, even though some of these participants were aware of their hypertension. If objective measurements would have been used, and participants would have been categorized; accordingly, being confronted with their compromised health status may have motivated them to change their behavior to a larger extent. Accurate classification of the 22 participants to group E may therefore have resulted in larger differences between the subgroups. This underscores that caution should be exercised when using self-reported data for personalized services. Misreporting may in general have consequences for the success of personalized nutrition programs if these programs rely on self-reported data. In addition, an inherent limitation to the use of the bioelectrical impedance is hydration status, which may ultimately result in the misestimation of fat and fat-free body mass. This misestimation may be more prevalent in obese individuals due to differences in body water, relative to normal weight individuals [102]. We did attempt to minimize these limitations in our design where participants served as their own control, by guiding participants on the importance of consistent hydration, in the use of consistent equipment and similar timing of visits. Finally, although well-described and standardized, the procedure used for collecting dietary intake data was not internally validated. Another limitation in this study was the lack of a control arm in this study. As this study was conducted in a workforce setting, a naïve control was not possible due to the inability to blind participants to the intervention. However, a 10-week run-in period was part of this study, which provides an indication of behavior changes and health effects of being included in a clinical study and could therefore be used as a qualitative control. During this run-in period, insulin resistance parameters increased, suggesting a reduced health state during the run-in period. The health improvements during the intervention period can therefore be ascribed to the PSN program and are not merely the result of being involved in a clinical trial. In a follow-up study, the effects of the PSN program should be compared to a control group receiving general advice.

Last, the intervention took place in a workforce. Previous studies have shown that sorting beneficial health effects in a workforce is challenging, which includes issues such as fit with organizational values, work climate, (perceived) management support, low participation rates and restructuring [103–106]. This workforce setting may also explain the drop-out rate in this study, as other workplace prevention programs show high attrition rates of 30 to 50%, whilst more intensive participation in workforce programs has been correlated with a greater reduction in health risks [107–109].

4.2. Strengths

First, despite the challenges related to performing a study in a workforce setting, this setting is also a strength of this study. As the workforce setting is a potential implementation area for personalized nutrition programs, performing a study in such a setting provides a good indication of its effectiveness in real life. Even in this real-life situation, beneficial effects of a personalized nutrition program were found.

Second, the onboarding for this personalized nutrition program was also designed such that it was completely do-it-yourself and thus could be performed in an at-work or at-home setting. For blood collection, DBS cards were used and required only a few blood drops that were easily collected by finger pricks. Blood spot collection was completed unsupervised. The type of card used allowed for multiple samples to be collected from each card to help correct for under-sampling on a given card. Despite some of the limitations discussed above, this report demonstrates that a do-it-yourself personalized nutrition program can improve diet and markers of health status.

Third, the personalized nutrition program combined an online platform with feedback, advice, and contact with an RDN, which augmented the experience for participants. Additionally, previous research has shown that combining e-health with personal contact is more effective in realizing lifestyle behavior change [22,23].

Fourth, in this study, a mixed-meal challenge test was part of the baseline assessment and used as the basis for the personalized nutrition program. As this challenge test simulates consumption of a real meal and allows data capture on the postprandial state, it provides a more holistic view of the metabolic health status of an individual as compared to fasting measurements only [35,110]. A recent study by Berry et al. also showed the importance of postprandial measurements and the differences in postprandial glucose and lipid response to food between individuals [111].

Fifth, participants were offered personalized meals on weekdays for breakfast and lunch, whilst most personalized nutrition studies only offer recommendations and not the actual foods. This makes it easy to adhere to the personalized nutrition recommendations, at least during breakfast and lunch.

Last, the focus in this study was on the quality of the provided meals (ingredients, macronutrient quality, micronutrient content) and not the quantity of meals. The caloric content of meals was equal for all participants. Therefore, the results from this study showed the added value of a high-quality diet and not merely the effects of caloric restriction. Calorie intake did decrease during the intervention, but this was likely the result of the higher satiating properties of the healthy personalized foods.

5. CONCLUSIONS

In our study, we have shown that a PSN program on a workforce has positive effects on health behavior, body composition and markers of health status for groups A and G (as other groups were underrepresented in the study), thus showing that PSN programs can improve health outcomes. Our study suggests that personalized nutrition may enable changes in dietary intakes that have not occurred through public health recommendations, for example, the recommendation to reduce sodium intake by 20% [112]. Additionally, between-group

differences indicate that personalized dietary programs may be an effective approach in realizing targeted behavior change in specific health-compromised individuals or target groups. Considering these two aspects, the possibility exists that in the future, personalized nutrition may provide the tools and motivation to enable individuals to achieve recommendations and reduce the health and economic burden of chronic diseases.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Examples of SNP-based narratives; Table S2: Lifestyle factors, anthropometrics, vitals, clinical chemistry, and indices at baseline (week 0), after run-in (week 10), and after the intervention period (week 20) for the PP population.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy reasons.

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4

EFFECTS OF A 13-WEEK PERSONALIZED LIFESTYLE INTERVENTION BASED ON THE DIABETES SUBTYPE FOR PEOPLE WITH NEWLY DIAGNOSED TYPE 2 DIABETES

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ABSTRACT

A type 2 diabetes mellitus (T2DM) subtyping method that determines the T2DM phenotype based on an extended oral glucose tolerance test is proposed. It assigns participants to one of seven subtypes according to their β-cell function and the presence of hepatic and/or muscle insulin resistance. The effectiveness of this subtyping approach and subsequent personalized lifestyle treatment in ameliorating T2DM was assessed in a primary care setting. Sixty participants, newly diagnosed with (pre)diabetes type 2 and not taking diabetes medication, completed the intervention. Retrospectively collected data of 60 people with T2DM from usual care were used as controls. Bodyweight ($p < 0.01$) and HbA1c ($p < 0.01$) were significantly reduced after 13 weeks in the intervention group, but not in the usual care group. The intervention group achieved 75.0% diabetes remission after 13 weeks (fasting glucose ≤ 6.9 mmol/L and HbA1c <6.5% (48 mmol/mol)); for the usual care group, this was 22.0%. Lasting (two years) remission was especially achieved in subgroups with isolated hepatic insulin resistance. Our study shows that a personalized diagnosis and lifestyle intervention for T2DM in a primary care setting may be more effective in improving T2DM-related parameters than usual care, with long-term effects seen especially in subgroups with hepatic insulin resistance.

INTRODUCTION

The main pathophysiological defects in type 2 diabetes mellitus (T2DM) are insulin resistance (IR) of the liver, muscle, and adipose tissue, and reduced β-cell function (BCF) [1]. Current treatment primarily focuses on lowering blood glucose concentrations and glycated hemoglobin (HbA1c) levels instead of addressing the underlying pathophysiology. Therefore, limited effectiveness may be achieved in diabetes treatment, especially in the longer term [2–4]. Several studies have shown that lifestyle interventions have beneficial effects on glycemic control [5–7], and may even induce disease remission [8,9]. In the DiRECT trial, a primary-care-led weight management program for T2DM, 46% of the intervention participants achieved disease remission [3,4]. The remission rate appeared related to β-cell capacity [6], indicating that not all persons react similarly to such interventions. As T2DM is a multi-factorial disease affecting multiple organs, and because people differ in their genetics, phenotype, lifestyle, and environment, different mechanisms may underlie T2DM pathophysiology [10,11]. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are both pre-stages of T2DM, can occur both separately and simultaneously, and differ in prevalence [12]. Moreover, plasma insulin levels in response to an oral glucose tolerance test (OGTT) differ [13]. A greater impairment in first-phase insulin secretion, indicative of hepatic insulin resistance (HIR), can be found in individuals with isolated IFG. People with IGT show higher two-hour insulin and glucose concentrations, indicative of muscle insulin resistance (MIR) [14]. The cardiometabolic T2DM etiologies of systemic low-grade inflammation and lipid dysmetabolism differ between people with MIR and people with HIR [15]. These differences in underlying T2DM pathophysiology may explain the differences in the effectiveness of lifestyle interventions. Indeed, it has been shown that in people with prediabetes with relatively high fasting insulin, a low-fat diet is most effective for weight loss, whereas for people with prediabetes with relatively low fasting insulin, a low-carbohydrate diet is most effective [16]. Another study comparing the two-year effects of both a low-fat and a Mediterranean diet showed a larger improvement in BCF on a low-fat diet in people with HIR, whilst people with MIR or a combination of muscle and liver IR (CIR) benefitted more from a Mediterranean diet [17]. Moreover, it is known that MIR is best counteracted by physical exercise [18], whereas caloric restriction seems to be effective in reducing HIR [19]. Thus, the diabetic subtype can be used to personalize—and potentially increase—the efficacy of and adherence to lifestyle treatment for T2DM.

Herein, we propose a subtyping method that determines an individual's diabetic phenotype and establishes the underlying pathophysiology [20]. T2DM subtyping was conducted by performing a five-timepoint OGTT, quantifying plasma glucose and insulin concentrations at baseline and 30 min intervals up to two hours. The resulting data were used to determine indices indicative of pancreatic insulin secretion and muscle and liver insulin resistance.

Based on the T2DM subtype, a personalized diagnosis and subsequent tailored treatment were determined. Next, we assessed the effectiveness of this T2DM subtyping approach in ameliorating T2DM by the evaluation of HbA1c and fasting plasma glucose (FPG), as well as the associated risk factors, including body weight, in comparison to usual care. Additionally, we elucidated whether personalized interventions improved the diabetic phenotype and induced diabetes remission. This study took place in a primary care setting to assess the feasibility of this more personalized approach in a real-life setting. The intervention lasted 13 weeks, with a two-year follow-up.

2. MATERIALS AND METHODS

2.1. Study Population

Eighty-two participants with prediabetes or newly diagnosed T2DM (within the last 12 months), according to the Dutch general practitioners' standards, were recruited from eight primary care centers in Hillegom, the Netherlands. In the Netherlands, T2DM diagnosis is determined based on glucose values with two FPG of ≥7.0 mmol/L or one FPG of ≥7.0 mmol/L combined with non-FPG of ≥11.1 mmol/L on two different days, whereas prediabetes is defined as an FPG of ≥6.1 and <7.0 mmol/L and/or a non-FPG of ≥7.8 and <11.1 mmol/L. Participants were eligible for study participation if they were aged 30–80 years, and had a stable body mass index (BMI) between 25 and 35 kg/m^2. The exclusion criteria were the use of plasma glucose-lowering medication within the past year, the use of systemic corticosteroids and β-blockers in the past month, pancreatic or (late-onset) type 1 diabetes, and other medical conditions, including gastrointestinal dysfunction, psychiatric disorders, severe hypertension, and renal insufficiency. Of the 82 participants initially enrolled in the study, 16 were excluded after the baseline OGTT because of either very poor BCF (n = 8) or normal glucose metabolism (neither reduced BCF nor IR) (n = 8).

From the same primary care center, the data of 60 people with prediabetes or newly diagnosed T2DM in usual care, meeting the above-stated inclusion and exclusion criteria, i.e., aged 30–80 years, BMI between 25 and 35 kg/m^2, and no use of plasma glucose-lowering medication, were collected retrospectively as controls. The historic data included fewer people with prediabetes because there is no official monitoring protocol for prediabetes according to the Dutch general practitioners' standards [21], as a result of which registration and monitoring occurs less frequently. All participants gave written informed consent. The study protocol was approved by the Medical Ethics Committee Brabant (NL48742.028.14). The study was performed in accordance with the Declaration of Helsinki and good clinical practice and was registered at ClinicalTrails.gov (NCT02196350).

2.2. Study Design

This study was exploratory. At baseline, clinical chemistry, blood pressure, and anthropometric measurements (length, body weight, waist circumference, and fat percentage) were performed. Based on the T2DM subtype, participants were allocated to one of seven personalized lifestyle treatments. The 13-week intervention was supervised by a dietician and/or physiotherapist. All participants visited the general practitioner's assistant at baseline and in weeks 4, 8, and 13, and participants visited the dietician at baseline and in weeks 1, 2, 6, 10, and 13 for (personalized) dietary advice. Those participants allocated to a treatment including exercise visited the physiotherapist for supervised personalized exercise training three times a week for 13 weeks. After the 13-week intervention, the measurements were repeated, including an OGTT to determine changes in glucose metabolism and the T2DM subtype. After the 13-week intervention, the participants returned to standard primary care. Anthropometry and clinical chemistry were repeated one and two years after baseline. Healthcare providers were instructed to be reluctant in prescribing oral diabetes medication or insulin therapy during the study. The intervention group was compared with historic data from a control group that received usual care according to the Dutch general practitioners' standards [21]. This states to start with prescribing oral diabetes medication when the HbA1c target level of 7.0% (53 mmol/mol) is not reached with a non-drug treatment. For this study, diabetes remission was defined as: (a) Fasting glucose ≤ 6.9 mmol/L, (b) HbA1c < 6.5% (48 mmol/mol), (c) no use of glucose-lowering medication, and (d) meeting these targets at the 12- and 24-month follow-up [2]. Figure 1 provides an overview of the study design.

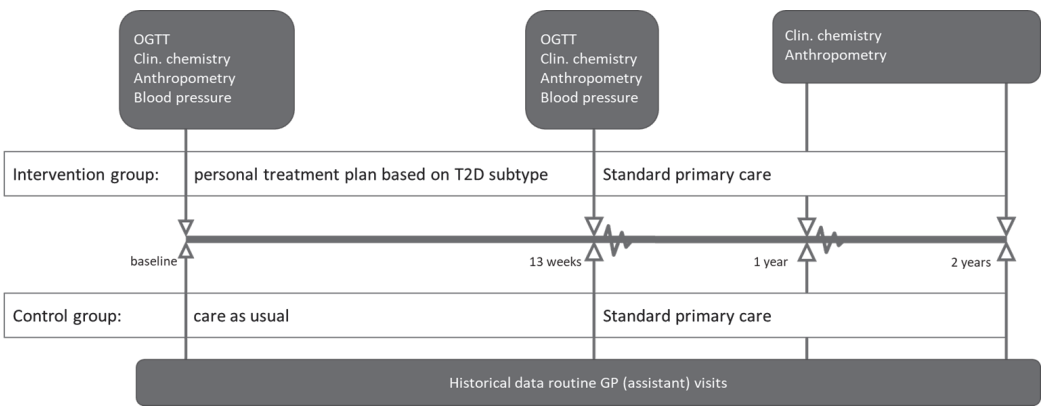

Figure 1. *Study design. GP = general practitioner; OGTT = oral glucose tolerance test; clin. chemistry = clinical chemistry (HbA1c, triglycerides and HDL, LDL, and total cholesterol). Anthropometry includes body height (only at baseline), body weight, waist circumference, and fat percentage.*

2.3. Clinical Chemistry and OGTT

After an overnight fast, blood samples were taken before (0 min) and at four time points after drinking a 75 g glucose solution (t = 30, 60, 90, and 120 min) to determine plasma glucose and insulin concentrations. HbA1c and lipids were assessed at baseline, 13 weeks, and at the

one- and two-year follow-up. OGTT and blood sampling were performed at the service center Elsbroek by AtalMedial in Hillegom, the Netherlands. Lab analyses were performed by AtalMedials' lab located in Spaarne Gasthuis Hospital, the Netherlands.

2.4. Subtyping Rationale

Glucose and insulin response to the OGTT was used to calculate the following indices: Disposition Index (DI) [22–24], Matsuda Index, Hepatic Insulin Resistance Index (HIRI) [25], and Muscle Insulin Sensitivity Index (MISI) [26]. Cut-off values for these indices, to distinguish between healthy and diabetic scores, were determined using data from ~1100 participants [27–29]. These cut-offs were calculated and validated using different subsets of healthy participants, participants with prediabetes (IFG, IGT, or both), and people with undiagnosed and clinically diagnosed T2DM. After calculating the indices, participants were assigned to one of seven subtypes according to BCF (moderate or low) and the presence of hepatic IR and/or muscle IR (Supplemental Table S1). Individuals with no IR and no BCF were excluded at baseline. If, after the intervention, participants reverted to no IR and no BCF, these participants were assigned to the "healthy" subtype.

2.5. Interventions

The HIR and CIR subgroup received a very-low-calorie diet (VLCD) for one week, using meal replacements (Modifast) three times a day (500 kcal/day), followed by a 12-week low-calorie diet (LCD; 1000 kcal/day) based on a personal meal plan provided by a dietician. Participants could opt for meal replacements for a maximum of one meal per day. Groups with poor BCF (PB), PB-HIR, or PB-CIR received 13 weeks of LCD, like the LCD of the HIR and CIR subgroups. Groups with MIR or PB-MIR followed an isocaloric diet (ICD), comprising normal food products.

In addition to the dietary intervention, participants in the HIR, PB, and PB-HIR subgroup were stimulated to adhere to the Dutch Norm for Healthy Physical Activity for overweight people (moderate exercise of 60 min/day). The CIR and PB-CIR subgroup were stimulated to adhere to the Dutch Norm for Physical Activity for one week, followed by 12 weeks of strength and endurance training (thrice a week for 60 min), supervised by a physiotherapist. The MIR and PB-MIR subgroups performed supervised strength and endurance training for 13 weeks.

2.6. Statistical Analysis

Complete case analysis was performed using only paired data at baseline and after 13 weeks. Two weighted linear mixed models were created, from which all statistical results were subsequently derived, using the "lmer" package [30]. One model included subtype as the main effect, whereas the other contained group. Both models included time as the main effect and the interaction of time with either group or subtype. Furthermore, both models included

the participant as a random factor. When fitting the models, statistical outliers were excluded when their standardized model residuals were further than three standard deviations away from 0. When applying these models, some variables were log10-transformed to account for heteroscedasticity in the model residuals. Type-III sum-of-squares *p*-values were calculated for the main effects using the "car" package, whereas *p*-values for the post hoc tests were calculated using the "emmeans" package [31]. Additionally, *p*-values of <0.05 were deemed statistically significant. The R Project for Statistical Computing software version 3.4.3 for Windows (The R Project for Statistical Computing, Auckland City, Auckland, New Zealand) was used for statistical analysis [32].

3. RESULTS

3.1. Baseline Characteristics

A total of 60 out of the 66 participants completed the intervention. At baseline, the intervention group had significantly lower HbA1c and FPG and significantly higher BMI compared with the usual care group (Table 1). Moreover, age tended to be higher in the usual care group *(p* = 0.06). In both groups, the average HbA1c levels were below the target level for people with type 2 diabetes, which is 7% (53 mmol/mol) in the Netherlands [21].

Table 1. *Baseline characteristics by treatment group.*

Characteristic	Usual Care	Intervention	*p*-Value
n	60	60	
Men/women (*n*)	34/26	29/31	NS
Age (years)	65.2 ± 9.7	63.4 ± 7.9	0.06
Body height (m)	1.73 ± 0.10	1.72 ± 0.10	NS
Bodyweight (kg)	90.4 ± 15.1	96.3 ± 16.1	NS
BMI	29.9 ± 5.0	32.6 ± 4.8	0.035
HbA1c (%) HbA1c (mmol/mol)	6.7 ± 3.4 49.7 ± 13.9	6.0 ± 2.8 42.6 ± 7.4	<0.001
FPG (mmol/L)	8.3 ± 4.0	7.0 ± 1.5	0.005
SBP (mmHg)	136 ± 19	137 ± 14	NS
DBP (mmHg)	82 ± 11	83 ± 10	NS
Total cholesterol (mmol/L)	5.9 ± 1.9 †	5.7 ± 1.1	NS
HDL-cholesterol (mmol/L)	1.3 ± 0.5 †	1.3 ± 0.3	NS
Triglycerides (mmol/L)	3.5 ± 5.4 †	2.2 ± 1.0	NS

Data are the mean ± standard deviation, unless otherwise indicated. † $n \approx 20$, not available for all controls and after outlier removal. BMI = body mass index; HbA1c = glycated hemoglobin; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; NS = not significant.

3.2. Intervention Effects Compared with Usual Care

After 13 weeks, body weight ($p < 0.001$) and HbA1c ($p < 0.001$) were significantly lower compared with baseline in the intervention group, whilst there were no significant changes in the usual care group (Supplemental Table S2). After one and two years of follow-up, body weight ($p < 0.001$) and HbA1c ($p < 0.001$ at one year and $p < 0.01$ at two years) remained significantly lower compared with baseline in the intervention group. In the usual care group, body weight ($p < 0.01$) was reduced compared with baseline at the two-year follow-up only. In the intervention group, total cholesterol (−0.47 mmol/L; $p < 0.01$), triglycerides (−0.58 mmol/L; $p < 0.001$), and waist circumference (−11 cm; $p < 0.001$) decreased after the intervention. These data were not available for the usual care group, as these markers are not measured regularly in usual care.

3.3. Diabetes Remission

Table 2 shows the fraction of participants who were classified as "in remission" for the usual care and intervention group. The results are shown as the fraction of participants diagnosed with T2DM at baseline, as our study population also included participants with prediabetes. The intervention group achieved significantly more T2DM remission after 13 weeks compared with the usual care group ($p = 0.0002$). In the intervention group, two participants started using glucose-lowering medication during the follow-up period of the study. For the usual care group, no medication data were available for follow-up, so it was unclear what proportion of participants were still in remission at the one- and two-year follow-ups.

For the intervention group, participants that achieved remission after 13 weeks showed significantly more weight loss than participants that did not achieve remission (−10.7 kg resp. −4.6 kg; $p < 0.001$). Of the participants with prediabetes at baseline, 89% remained prediabetic, whilst 11% progressed to T2DM during the study. Those participants that progressed to T2DM showed significantly less weight loss than participants that remained prediabetic ($p = 0.05$).

Table 2. *Remission data * for the intervention and usual care groups after the intervention (week 13) and at the one- and two-year follow-ups (week 52 and 104), expressed as the number and percentage of participants with T2DM at baseline **.*

	Usual care		**Intervention**	
	(*n* = 41)	**(%)**	**(*n* = 25)**	**(%)**
13 weeks	5	22.0	19	75.0
52 weeks	-	-	13	52.4
104 weeks	-	-	7	28.6

* Remission was defined as fasting plasma glucose ≤6.9 mmol/L and HbA1c <6.5% (48 mmol/mol), no use of glucose-lowering medication, and meeting these targets at 12 and 24 months of follow-up; medication data were not available at follow-up for the usual care group. ** In other words, subjects with prediabetes at baseline were excluded from this table, as the remission definition does not apply to people with prediabetes.

3.4. Changes in the Diabetic Phenotype in the Intervention Group

At baseline, 11 participants had hepatic IR (HIR), 7 participants had muscle and hepatic IR (combined IR; CIR), 9 participants had isolated poor BCF (PB), 28 participants had PB-HIR, and 5 participants had PB-CIR. At baseline, there were no participants with a healthy, MIR, or PB-MIR subtype. A substantial redistribution of participants over the subtypes was found after 13 weeks of intervention (Figure 2). The most noticeable trend was seen for the HIR subtype, with 55% of the participants converting into a healthy subtype after the intervention. For the PB-HIR and CIR subtype this was 29%, whereas for the PB and PB-CIR subtypes, it was 22% and 20%, respectively.

In total, 32% of the participants (n = 19) obtained a healthy subtype (normal BCF without IR) after 13 weeks of intervention, of which 7 participants met the criteria for T2DM remission, 11 had prediabetes at baseline, and one participant reached a HbA1c of 5.4% (36 mmol/mol) and FPG of 7.0 mmol/L at 13 weeks. Including the participant with borderline remission and a healthy subtype, in total, 10 participants could be classified as T2DM after 13 weeks of intervention, of which 6 had the PB-HIR subtype and 3 the PB-CIR subtype.

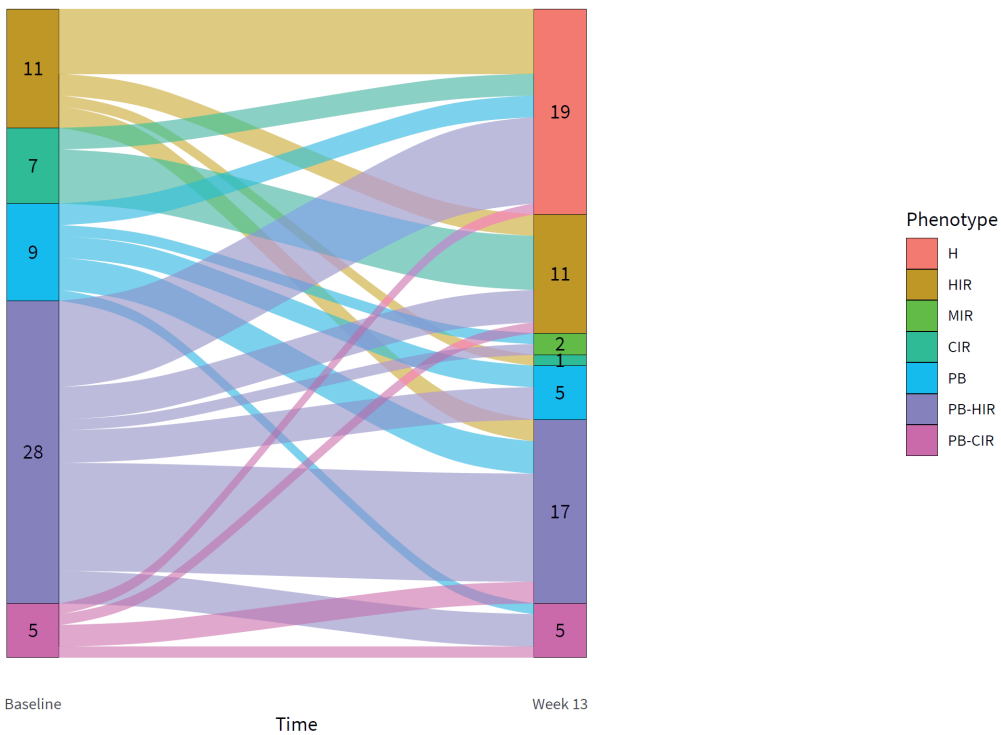

Figure 2. *Flow diagram showing the shift in subtypes for participants from baseline to 13 weeks. A shift upwards illustrates a shift toward a less complex phenotype. H = healthy; HIR = moderate BCF and liver IR; MIR = moderate BCF and muscle IR; CIR = moderate BCF and combined IR; PB = low BCF and no IR; PB-HIR = low BCF and liver IR; PB-CIR = low BCF and combined IR.*

3.5. Changes in the Glucose Metabolism in the Intervention Group

Liver IR significantly improved (HIRI of −80.2; $p < 0.001$) after 13 weeks. Postprandial glucose (PPG) decreased significantly (−1.34 mmol/L; $p < 0.001$) after 13 weeks. The disposition index and MISI did not change over time ($p = 0.231$, resp. $p = 0.945$).

Furthermore, the 13-week intervention significantly decreased HIRI in all subtypes with liver IR (unknown for subgroup PB-CIR, as no *p*-value could be calculated due to missing data; Table 3). FPG decreased in two of these subgroups (HIR and PB-HIR).

Table 3. *Changes in oral glucose tolerance test response from baseline to 13 weeks (end of intervention) for the main type 2 diabetes subtypes.*

Subtype	FPG	PPG	DI	HIRI	MISI
HIR ($n = 11$)	−1.2 **	−1.1	2.19	−1145 **	0.41
CIR ($n = 7$)	−0.3	−3.1 *	1.44	−619 *	−1.71 †
PB ($n = 9$)	0.3	0.2	0.33	138	0.09
PB-HIR ($n = 28$)	−1.2 **	−0.3	0.80 *	−22 **	1.58 **
PB-CIR ($n = 5$)	−0.6	−8.4 †	0.87	2525 †	−2.16 ‡

The data are deltas between baseline and 13 weeks of intervention. FPG = fasting plasma glucose; PPG = postprandial glucose; DI = disposition index; HIRI = hepatic insulin resistance index; MISI = muscle insulin sensitivity index; HIR = moderate BCF and liver IR; CIR = moderate BCF and combined IR; PB = low BCF and no IR; PB-HIR = low BCF and liver IR; PB-CIR = low BCF and combined IR. * $p < 0.01$ and ** $p < 0.001$ compared with baseline; † no *p*-value available due to missing data; ‡ trend toward a decrease ($p = 0.0590$).

Unexpectedly, MISI increased in the PB-HIR subgroup, indicating a decrease in muscle insulin sensitivity, although the mean MISI was still within the healthy range (−2.87 ± 1.27). Postprandial glucose improved in the CIR subgroup only. The disposition index only improved in the PB-HIR subgroup.

3.6. Long-Term Intervention Effects

All subgroups showed a significant reduction in body weight after the intervention, which was maintained at one and two years of follow-up for all subgroups, except for the group with PB-CIR (+3.3 kg; $p < 0.05$) (Table 4).

In the HIR and PB-HIR subgroups, FPG and HbA1c decreased after the intervention, which was maintained up to two years of follow-up. In the CIR subgroup, HbA1c was significantly reduced after the intervention, but this effect was not maintained at follow-up. For all other subgroups, no significant changes in FPG or HbA1c were found.

Table 4. *Changes in body weight, FPG, and HbA1c from baseline (week 0) to the end of the intervention (week 13) and to the one- and two-year follow-ups (weeks 52 and 104) for the type 2 diabetes subtypes.*

	HIR (***n*** **= 11)**	**CIR** (***n*** **= 7)**	**PB** (***n*** **= 9)**	**PB-HIR** (***n*** **= 28)**	**PB-CIR** (***n*** **= 5)**
Bodyweight (kg)					
Weeks 0–13	−10.2 ***	−13.1 ***	−5.6 **	−8.8 ***	−5.7 *
Weeks 0–52	−9.1 ***	−7.3 **	−4.8 ***	−6.0 ***	2.0
Weeks 0–104	−8.4 ***	−7.1 **	−2.3 *	−6.0 ***	3.3 *
Fasting glucose (mmol/L)					
Weeks 0–13	−1.1 ***	−0.3	0.3	−1.1 ***	−0.5
Weeks 0–52	−1.3 ***	−0.2	0.0	−0.7 ***	0.4
Weeks 0–104	−1.0 ***	−0.2	0.4	−0.7 ***	−0.3
HbA1c (mmol/mol)					
Weeks 0–13	−3.4 ***	−3.3 *	0.0	−6.2 ***	−2.2
Weeks 0–52	−4.3 **	−1.3	−1.3	−4.9 ***	−1.5
Weeks 0–104	−2.4 *	−0.4	1.8	−2.5 **	−1.3

The data are deltas comparing baseline to week 13 (end of intervention), week 52 (one year follow-up), and week 104 (two years follow-up). HIR = moderate BCF and liver IR; CIR = moderate BCF and combined IR; PB = low BCF and no IR; PB-HIR = low BCF and liver IR; PB-CIR = low BCF and combined IR. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with baseline.

4. DISCUSSION

In this study, we showed that diabetes subtyping and subsequent tailored lifestyle interventions in a primary care setting are more effective in improving T2DM-related parameters than usual care. Bodyweight and HbA1c were significantly reduced after 13 weeks of intervention, whilst no changes in these markers were seen with usual care. Additionally, the improvements in health status were maintained up to two years after the intervention. Our results suggest that a (V)LCD may be more effective in improving liver IR, whilst resistance training may be more effective in improving muscle IR.

Unique to our study was the use of an extended OGTT in a primary care setting for identifying the diabetic phenotype and subsequently using this knowledge for a tailored lifestyle treatment. Various clinical studies have shown that persons with T2DM may differ in their metabolic profile, resulting in differential responses to lifestyle interventions [13,15,17,33–36]. However, in these studies, participants were assigned to a dietary pattern at random and subtype effects were identified retrospectively. To the best of our knowledge, this is the first study in which the metabolic profiling of people with T2DM was performed prospectively

and used for a phenotype-based sub-diagnosis and adjacent tailored lifestyle treatment in a real-life primary care setting.

Our results suggest that these tailored treatments indeed induce differential effects. The specific improvements in HIRI and FPG for the groups with liver IR, and the improvements in PPG in the groups with combined IR (CIR), suggest that the tailored treatment may have added value over a one-size-fits-all approach. However, as there were no participants with isolated muscle IR (with or without low BCF), future research is needed to investigate the effects of a solely physical activity intervention in people with muscle IR. Previous research has shown that improving MISI is more difficult or may take longer [36,37]. The lack of effect, or even a small negative effect in the PB-HIRI group, on MISI in our study may be a result of weight loss. Weight loss may have included a loss of muscle mass, which may negatively affect MISI. However, in the PROBE trial, the lack of effect on MISI coincided with an improved muscle mass [36].

Average weight loss in our study after one year was 7.1 kg, and this resulted in improvements in T2DM-related health parameters. Caloric restriction has been shown to reduce pancreatic and hepatic fat content and hepatic IR and improve BCF [19,38]. In our study, weight loss was strongly correlated with achieving remission, with an average weight loss of −10.7 kg in the group that achieved remission and −4.7 kg in the group without remission. These results indicate a relationship between T2DM remission achievement and weight loss, as also shown in the DiRECT trial [3]. Modest weight loss of 5%–10% has also been previously linked to improvements in cardiovascular risk factors, including HbA1c [39]. Non-responders predominantly had a complex phenotype with combined IR, decreased BCF, or both, indicating that achieving remission is more difficult with a more progressed disease status. Karter et al. observed an association between the rate of remission and years since diagnosis [40], and Taylor et al. linked non-response to a lifestyle intervention to a more advanced, irreversible stage of β-cell dysfunction. In our study, subgroups with combined insulin resistance with or without poor BCF or poor BCF only (CIR, PB, and PB-CIR) showed only short-term or no improvements in FPG or HbA1c [6], whereas subgroups with hepatic insulin resistance with or without decreased BCF (HIR and PB-HIR) had long-term improvements in FPG and HbA1c. Interestingly, persons with combined insulin resistance (CIR) did achieve a sustained bodyweight reduction of 7 kg after two years of follow-up that did not result in reduced hyperglycemia. Therefore, the subgroups with isolated liver IR (HIR and PB-HIR) benefitted most from the lifestyle treatment, as shown by improved bodyweight, HIRI, FPG, and HbA1c after the intervention period, and improved FPG and HbA1c after one and two years of follow-up.

The percentage of participants in remission after the intervention was 75.0%. However, when looking at the diabetic phenotype of the included participants, based on indices for organ-specific insulin sensitivity and β-cell function, only 28% of the participants with T2DM at baseline had a fully remitted and healthy subtype (normal BCF and no IR) after the

intervention. T2DM is indeed a multi-factorial disease affecting multiple organs, and normalization of HbA1c and/or FPG levels can still coincide with reduced organ function and β-cell dysfunction [41]. It is therefore recommended for individuals who achieve remission to remain under the supervision of healthcare professionals [42].

Increasing focus on the functioning of organs involved in the pathophysiology of T2DM (liver, adipose tissue, skeletal muscle, and pancreas) may therefore provide more insight into the effects of interventions and disease status, instead of merely focusing on remission numbers. We therefore suggest performing an extended OGTT to assess diabetes pathophysiology so that disease progression or regression before and after an intervention can be more accurately determined over time. Indeed, in a pilot study using the same subtyping methodology in a population with a longer T2DM disease duration, none of the participants were able to achieve a healthy subtype, even though improvements in HbA1c and FPG were observed [37]. Additionally, the diabetes subtyping methodology allows for a more tailored lifestyle intervention, which may improve intervention success. For this, our subtyping method can be used, which uses blood glucose and insulin response to a five-point OGTT as a measure of diabetes pathophysiology [20,43]. Besides our subtyping model, other models exist, using established T2DM genetic loci to identify several diabetic phenotypes [44], using clinical parameters to cluster adult-onset diabetes [45,46], or using patterns of specific glycemic responses called “glucotypes” [47]. The importance of differences in organ function was also suggested in the Diogenes and Maastricht studies, which showed an altered metabolic profile in persons with obesity and liver IR compared with persons with obesity and muscle IR [15,48,49]. However, our subtyping method is, to the best of our knowledge, the first that provides a complete picture of the underlying pathophysiology of T2DM and offers the opportunity for tailored treatment.

A few limitations need to be discussed. An important limitation of this explorative study was that participants in the usual care group were not accurately matched with the intervention group for BMI and age, due to a limited available patient database. Additionally, or maybe consequently, the usual care group had higher baseline FPG and HbA1c values compared with the intervention group. Additionally, as OGTTs are not performed in usual care, no data on type 2 diabetes subtypes and the comparability of the distribution thereof with the intervention group were available. Considering the higher baseline FPG and HbA1c values, the participants in the usual care group, although newly diagnosed, without treatment for type 2 diabetes and with an average HbA1c level below the target, could all have had a poor BCF, which would explain the scarce response in this group. Furthermore, no data on medication were available for the usual care group, except for baseline, where oral medication was used as the exclusion criterium. Possibly, in the usual care group, the use of glucose-lowering medication could have started throughout the trial. These differences between the usual care and intervention groups may have influenced our results. A future efficacy study with a prospective control arm randomized for BMI, age, FPG, HbA1c, and BCF status, as well as

careful registration of medicine use is needed to confirm the current results from diabetes subtyping and tailored lifestyle intervention.

In the Netherlands, people are screened for T2DM by determining FPG levels and sometimes HbA1c levels. As 2 h blood glucose is not measured, participants with isolated IGT, which is defined as 2 h glucose levels of 7.8–11.1 mmol [50], are missed. This may have caused the underrepresentation of participants with muscle IR in our study. To improve the early detection of and treatment for participants with isolated IGT, we suggest always performing an OGTT or at least measuring 2 h blood glucose levels.

In the intervention group, the number of participants was relatively small per diabetes subtype, especially for the PB-CIR, CIR, and PB groups. Despite the small diabetes subtype groups, we were still able to reach statistical significance for some of the variables, providing interesting insights into the underlying pathophysiology of type 2 diabetes and how lifestyle interventions can interact with this. For a follow-up study, a larger study population is required to confirm and validate these findings. It will remain difficult, however, to influence equal distribution over the diabetes subtypes, as this follows from the OGTT. Lastly, the frequency of visits to a healthcare professional, including visits to the GP assistant, as well as to dieticians and/or physiotherapists, was probably lower in the control group as compared with the intervention group, which could have resulted in differences in intervention adherence, thereby affecting the study results. However, this more intensive guidance, as well as referral to lifestyle professionals such as dieticians and physiotherapists may be required to help people with newly diagnosed T2DM to initiate behavior change.

5. CONCLUSIONS

This was the first study to provide tailored treatment based on the diabetic phenotype of people with T2DM in a primary care setting. The tailored approach resulted in differential effects on T2DM phenotypes, with the largest and most persistent improvement in participants with isolated liver IR (with or without low BCF). Our results suggest that a (V)LCD may be more effective in improving liver IR, whilst resistance training may be more effective in improving muscle IR. Future research, including participants with isolated muscle IR, a prospective control arm matching the intervention arm, and a larger number of study participants to have larger subgroups of diabetes subtypes, should confirm these findings. Even though diabetes remission was achieved by most participants in the intervention group, organ-specific IR and BCF were not fully recovered. This calls for continued monitoring to avoid relapse, and long-term adherence to a tailored-lifestyle treatment may be required for people who achieve T2DM remission. Lastly, this study showed that the tailored approach can be implemented in current primary care and can result in remission or reversal of the disease in the first three months after T2DM diagnosis.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1: Table S1: Deviating indices and associated treatment plan for all seven type 2 diabetes subtypes and the "healthy" subgroup; Table S2: Means (SDs) and significant changes in the variables after 13 weeks of intervention and one or two years of follow-up for the usual care and intervention groups.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

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THE EFFECT OF A LIFESTYLE INTERVENTION ON TYPE 2 DIABETES PATHOPHYSIOLOGY AND REMISSION: THE STEVENSHOF PILOT STUDY

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ABSTRACT

Although lifestyle interventions can lead to diabetes remission, it is unclear to what extent type 2 diabetes (T2D) remission alters or improves the underlying pathophysiology of the disease. Here, we assess the effects of a lifestyle intervention on T2D reversal or remission and the effects on the underlying pathology. In a Dutch primary care setting, 15 adults with an average T2D duration of 13.4 years who were (pharmacologically) treated for T2D received a diabetes subtyping ("diabetyping") lifestyle intervention (DLI) for six months, aiming for T2D remission. T2D subtype was determined based on an OGTT. Insulin and sulphonyl urea (SU) derivative treatment could be terminated for all participants. Body weight, waist/hip ratio, triglyceride levels, HbA1c, fasting, and 2h glucose were significantly improved after three and six months of intervention. Remission and reversal were achieved in two and three participants, respectively. Indices of insulin resistance and beta cell capacity improved, but never reached healthy values, resulting in unchanged T2D subtypes. Our study implies that achieving diabetes remission in individuals with a longer T2D duration is possible, but underlying pathology is only minimally affected, possibly due to an impaired beta cell function. Thus, even when T2D remission is achieved, patients need to continue adhering to lifestyle therapy.

1. INTRODUCTION

Type 2 diabetes (T2D) has become a global health burden [1]. T2D refers to a metabolic glucose dysregulation resulting from insulin resistance (IR) and inadequate insulin secretion [2], although the etiology of T2D is highly heterogeneous [3]. T2D is preceded by insulin resistance and ensues when the pancreas becomes unable to compensate for insulin resistance, resulting in glucose intolerance and hyperglycemia [4]. Prolonged hyperglycemia can induce glucotoxicity, which causes beta cell dysfunction and altered beta cell mass, contributing to further deterioration of T2D [5]. The primary pathophysiological defects in T2D are IR of the liver, muscle, and/or adipose tissue, as well as impaired pancreatic beta cell function (BCF) [6]. The severity of IR in insulin-sensitive cells is not uniform, and may differ among various tissues [7,8]. The development of T2D results from the interaction of a person's genetic makeup with their environment [9], with risk factors being obesity, unhealthy diet, and physical inactivity [10].

While T2D (medical) treatment is aimed at preventing or delaying cardiovascular complications [11], weight loss and lifestyle changes can reverse the pathophysiological processes underlying T2D, and remission can be achieved [12–14]. Remission of T2D is defined as a state in which an individual previously diagnosed with T2D has normal glucose values in the absence of pharmacological therapy, either for a defined period or without a temporal definition [15,16], although great variability exists in the exact definition [17,18]. The most widely used definition of T2D remission was published in a consensus report in 2009 and includes: (1) the absence of glucose-lowering therapy; (2) normoglycemia; and (3) for a duration of $\geq$ 1 year [16]. The various definitions make T2D remission difficult to effectively use as an outcome in clinical care [19], while, for the individual with T2D, remission can be an important goal in striving to be freed from diabetes [14]. Indeed, in a clinical setting, halting disease progression or improving glucose homeostasis could already be considered a clinically meaningful outcome. Therefore, we define T2D reversal by reaching target values for HbA1c and fasting plasma glucose (FPG) with reduced medication or attaining normalized HbA1c and FPG values with unchanged medication.

Although consensus exists on the importance of lifestyle management and diabetes self-management education and support, with a chance for remission, T2D is mostly treated with medication [11]. Lifestyle strategies that can be used to achieve remission of T2D often include weight loss, which is especially effective when the beta cells have not yet been irreversibly damaged [14]. Due to the differences in underlying T2D pathophysiology and etiology, specific therapeutic approaches may be beneficial. It has been shown that the diabetic phenotype, that is, the T2D subtype based on the location of the IR (i.e., muscle, liver, or both) and remaining BCF, may determine the response to different dietary interventions [20]. Research shows that hepatic insulin resistance can be improved via a short, intense, and very low-calorie diet [39, 46]. In the longer term, hepatic insulin resistance as well as BCF can be improved by a low carbohydrate diet [21,22]. Muscle insulin resistance

can be addressed using a Mediterranean diet [20]. By measuring glucose and insulin concentrations at 30 min intervals from baseline up to two hours in response to an oral glucose tolerance test (OGTT), various indices indicative of pancreatic BCF and muscle and hepatic IR can be determined, and the T2D subtype can be established [7]. This provides insight into which pathophysiological defects should be addressed [23] and provides a basis for a personalized (lifestyle) treatment that is more specific than the generic advice to eat healthy and increase physical activity.

In this study, we propose the Diabetyping Lifestyle Intervention (DLI), in which the OGTT is used to determine the diabetic subtype in individuals with T2D. Information about the diabetic subtype was combined with clinical parameters and personal preferences to provide a personalized treatment plan, aiming for T2D remission or reversal. Although lifestyle interventions can result in diabetes remission, it is unclear to what extent T2D remission alters or improves the underlying pathophysiology of the disease. In this exploratory implementation study, in which the DLI was used in primary care, we wanted to assess whether the DLI could lead to reversal or remission of T2D, and what the effects would be on the underlying T2D pathophysiology and subtype.

2. MATERIALS AND METHODS

2.1. Participants

Fifteen participants that were diagnosed with T2D according to the Dutch general practitioner standards [24] were recruited from two primary care centers in the Stevenshof area (Leiden), the Netherlands. T2D in the Netherlands is clinically diagnosed when fasting blood glucose values are ≥ 7 mmol/L on two different occasions, or when a random blood glucose value is ≥ 11.1 mmol/L in combination with symptoms of hyperglycemia [24]. People with T2D were eligible for participation if they were on the verge of a change regarding their T2D, namely newly diagnosed with T2D or about to start metformin, a second oral drug (like sulphonyl urea (SU) derivatives) or an injectable drug (insulin or GLP-1). Participants had to be aged 30 to 80 years and have a stable body mass index (BMI) between 25 and 35 kg/m^2. Exclusion criteria were limiting circumstances, such as dialysis, under the treatment of a psychiatrist, or being unable to attend most meetings. Taking blood pressure and lipid-lowering medication was allowed. Written informed consent was obtained from all patients. The study protocol was approved by the Medical Ethics Committee Brabant (NL67846.028.18; 8 January 2019). The study was performed in accordance with the Declaration of Helsinki and good clinical practice. The study was registered at the Netherlands Trial Register (https://www.trialregister.nl/; NL-7509; accessed on 7 June 2021).

2.2. Study Design

This study was an exploratory implementation study regarding the feasibility of the DLI in primary care. The DLI started with clinical measurements performed by caregivers. Clinical measurements at baseline consisted of clinical chemistry, blood pressure, and anthropometric measurements. An OGTT was performed to assign subjects to one of eight T2D subtypes based on a combination of their BCF and the presence of hepatic and/or muscle IR. During the OGTT, subjects had a medication review with the pharmacist and a dietary review with the dietician. Results from the first OGTT, other clinical measurements, and medication and dietary review were discussed during a multidisciplinary meeting between a nurse practitioner, general practitioner, dietician, and pharmacist. Next, the nurse practitioner and dietician discussed the results with the patient in a shared decision-making process. This resulted in a personal DLI treatment plan, in which the diabetes subtype, other clinical parameters, current lifestyle behavior, and personal preferences were considered, which contained dietary, physical activity, sleep, stress, and medication related advice. During the six-month DLI, there was regular contact between the patient, nurse practitioner, and/or dietician in face-to-face consults, via e-mail, and via telephone. Subjects were supplied with a glucose meter to monitor the effect of their lifestyle adaptation on glucose levels. Baseline measurements were repeated at three and six months for progress monitoring. In this manuscript, we focus on the clinical and pathophysiological methods, data, and results. A full description of the study methods can be found at the Netherlands Trial Register (https://www.trialregister.nl/; NL-7509; accessed on 7 June 2021).

2.3. Clinical Measures, Anthropometrics, and OGTT

At baseline, and after three and six months of intervention, subjects underwent an OGTT. After an overnight fast for at least ten hours and not taking blood glucose lowering medication after 20:00 the day before, blood samples were taken before (t = 0 min) and at four time points after (t = 30, 60, 90, and 120 min) drinking a 75 g glucose solution (Top Star 75, Top labs, M. Feira, Portugal) to determine plasma glucose and insulin concentrations. OGTT guidelines as used in standard clinical practice were used. No specific instructions on carbohydrate intake prior to the OGTT were provided, as suggested by Klein et al. (2021) [25]. At three and six months, diet was in line with the dietary instructions provided to the participants. At baseline, all participants consumed a western diet (> 200 g of carbs per day). From the t = 0 blood sample, HbA1c (Menari Ha-8180, Medicon, Newry, Ireland; intra-assay coefficient of variation (CV): 1.3%; CV-inter: 1.4%), HDL, LDL, total cholesterol, and triglycerides (TG) were determined (Cobas C501 chemistry analyzer, Roche Diagnostics, Mannheim, Germany). For glucose, an enzymatic assay with hexokinase was performed using the Cobas C501 chemistry analyzer (Roche Diagnostics, Mannheim, Germany; CV-intra: 1.0%; CV-inter: 1.5%). Insulin measurement was performed by IJsselland Hospital, Capelle aan den IJssel, the Netherlands. For insulin, an immunoradiometric assay was performed using the BI-Insulin-IRMA kit from CisBio (CisBio International, Gif-sur-Yvette,

France; CV-intra: 5.0%; CV-inter: 6.8%). At baseline, subjects collected morning urine for determining kidney functioning using the estimated glomerular filtration rate (eGFR) and albumin/creatinine ratio by measuring creatinine and albumin (Cobas C501 chemistry analyzer, Roche Diagnostics, Mannheim, Germany). OGTT and blood sampling, as well as lab analyses, were performed by SCAL Medical Diagnostics, Leiden, the Netherlands. Blood pressure and anthropometrics (body weight and length, waist and hip circumference) were measured by caregivers at all three test days.

2.4. Diabetyping

Blood glucose and insulin concentrations from the five-point OGTT were used to calculate the following three indices used for diabetyping (Table 1): (1) the hepatic insulin resistance index (HIRI) to quantify hepatic IR; (2) the muscle insulin sensitivity index (MISI) to quantify muscle IR; and (3) the disposition index [7,26–28] as a measure of pancreatic BCF. Using a combination of hepatic IR, muscle IR, combined IR, or no IR with normal or impaired BCF resulted in a total of eight subgroups. The cutoff values for each of these indices to distinguish between healthy and diabetic scores were determined using the data of DiOGenes [29], CorDiOPrev [30], and two Phenflex [31,16] studies (about 1100 subjects in total). These values were calculated and validated using different subsets of healthy subjects, subjects with prediabetes (impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both), and patients with undiagnosed and clinically diagnosed T2D. Patients with no IR and normal BCF were assigned healthy.

Table 1. *Mathematical formulas and indication for glucose- and insulin-derived indices used for diabetyping [7–10].*

Index	Formula	Indicates
Matsuda index	$10{,}000/\sqrt{(fG \times fI)(mG \times mI)}$	Poor systemic insulin sensitivity
Disposition index	$[AUC_{30min\ insulin}/AUC_{30min\ glucose}] \times$ Matsuda index	Impaired β-cell function
Hepatic Insulin Resistance Index (HIRI)	$fG \times fI$	Hepatic insulin resistance
Muscle Insulin Sensitivity Index (MISI)	$(\Delta G/\Delta t)/mI$	Muscle insulin resistance

fG = fasting plasma glucose; fI = fasting plasma insulin; AUC = area under the curve; mG = mean plasma glucose; mI = mean plasma insulin; ΔG = delta glucose; Δt = delta time.

2.5. Dietary Interventions

Diets were chosen based on the diabetic subtype. The first aim was to decrease hepatic IR, thereafter, to improve BCF, followed by muscle IR. Hepatic IR was addressed by a short, intense, and very low-calorie diet of one week solely vegetables. BCF and hepatic IR were aimed to be (further) improved by a low carbohydrate diet (approximately 75 g of carbs per day). Muscle IR was addressed using a Mediterranean diet (vegetables, 100–150 g of wholegrains, protein, nuts, dairy, cheese, oil; three meals per day). The Mediterranean diet was also used as a healthy diet for long-term follow-up after the low carbohydrate diet.

At baseline, all except one participant showed hepatic IR, either isolated or in combination with impaired BCF. Therefore, all participants, but one, were recommended to follow a one-week, short, and intense vegetable diet, followed by a low carbohydrate diet (75 g/day) up to three months. One participant had no hepatic IR, and one had a complicated medical history and therefore skipped the vegetable diet to start the low carbohydrate diet directly. After three months of intervention, oral glucose tolerance testing was used to assess progress. If insulin resistance and other measured parameters were improved, participants were gradually transferred to a Mediterranean diet (one unit of 20 g of carbs was added every two weeks up to 150 g of wholefood, wholegrain products). If needed, the dietary interventions were intensified by exercise and intermittent fasting (16–18h fast, eight hour eating window, two low-carb meals per day). When participants relapsed into old habits, they were recommended to follow a vegetable diet for 2–4 days or do intermittent fasting, next to extra lifestyle coaching by a nurse practitioner and dietitian. If participants tended to drop out, a cycle diet was used, consisting of 3–4 days of solely vegetables, 3–4 weeks of a low carbohydrate diet, and one week of eating according to the Dutch dietary guidelines, with a maximum of 125 g of carbs.

2.6. Diabetes Remission and Reversal

For this study, T2D remission was defined as: (a) fasting glucose ≤ 6.9 mmol/L, (b) HbA1c < 48 mmol/mol, and (c) no glucose-lowering medication at the outcome assessments [32]. T2D reversal was defined as attaining target values for HbA1c (≤ 53 mmol/mol) and fasting glucose (< 8.0 mmol/L) [1] with reduced medication (taking fewer types or a lower dose of glucose-lowering medication at three or six months compared to the start of the trial) or attaining normalized HbA1c (< 48 mmol/mol) and fasting glucose (≤ 6.9 mmol/L) with equal medication at three or six months compared to the start of the trial.

2.7. Statistical Analysis

A complete case analysis was performed using paired data at baseline and after three and six months of intervention. Two linear mixed models were created, from which all statistical results were subsequently derived using the lmer package [33]. The first model was created for data measured during the OGTT, namely glucose and insulin. The main effects for the

first model were study time (0, three, and six months), OGTT time (0, 30, 60, 90, and 120 min), and their interaction. For the second model, the main effect was study time. Additionally, both models included the participant as a random factor. When applying these models, some variables were log10 transformed to account for the non-normality of model residuals. Statistical outliers were removed by excluding samples that had a standardized residual at a distance greater than three standard deviations from 0. Type-III sum-of-squares *p*-values were calculated for the main effects using the car package, while *p*-values for the post hoc tests were calculated using the emmeans package [34,35]. No multiple testing correction was applied; *p*-values < 0.05 were deemed statistically significant. All statistical analyses and data visualization was performed using The R Project for Statistical Computing software version 4.0.3 for Windows [36]. The ggplot2 and ggalluvial packages were used for data visualization [37,38].

***Table 2**. Baseline characteristics.*

Variable	Mean (SD)
Men/women (*n*)	10/5
Age (years)	59.6 (8.8)
Years diagnosed with T2D	13.4 (5.2)
Body height (m)	1.73 (0.09)
Body weight (kg)	102.6 (13.0)
BMI (kg/m^2)	34.1 (3.5)
HbA1c (mmol/mol)	67.6 (12.3)
FPG (mmol/L)	11.98 (3.22)
PPG (mmol/L)	21.38 (4.46)
Fasting plasma insulin (mU/L)	23.9 (11.8)
SBP (mmHg)	136.7 (14.0)
DBP (mmHg)	79.8 (7.1)
Total cholesterol (mmol/L)	4.03 (0.56)
LDL cholesterol (mmol/L)	2.02 (1.01)
HDL cholesterol (mmol/L)	1.00 (0.19)
Triglycerides (mmol/L)	2.81 (1.51)
Albumin/creatinine ratio	4.96 (8.46)
eGFR (mL/min)	91.7 (15.7)

Data are means ± standard deviations (SDs), unless otherwise indicated. BMI = body mass index; FPG = fasting plasma glucose; PPG = postprandial glucose at 2 h; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low density lipoprotein; HDL = high density lipoprotein; eGFR = estimated globular filtration rate.

3. RESULTS

All 15 participants completed the intervention. Table 2 shows the baseline characteristics for the study population. Besides being diagnosed with type 2 diabetes, all participants met the criteria for metabolic syndrome [39].

3.1. Intervention Effects

After three months of intervention, body weight ($p < 0.001$), BMI ($p < 0.001$), waist circumference ($p < 0.001$), HbA1c ($p < 0.001$), FPG ($p < 0.001$), systolic blood pressure (SBP) ($p = 0.016$), and triglycerides ($p = 0.002$) were significantly lower and HDL cholesterol was significantly higher ($p = 0.048$) compared to baseline (Table 3). The improvement in these markers was maintained after six months of intervention, except for SBP. Although HbA1c and FPG were significantly lower after six months of intervention compared to baseline, a significant increase was seen from three to six months of intervention (HbA1c $p = 0.005$; FPG $p = 0.005$).

Table 3. Means, standard deviations (SDs), and significant changes in variables from baseline to three months of intervention, from baseline to six months of intervention, and from three months to six months of intervention.

Variable	Mean (SD)		
	Baseline	**Three Months**	**Six Months**
Body weight (kg)	102.6 (13.0)	92.5 (10.3) [a]	91.7 (10.5) [a]
BMI (kg/m^2)	34.1 (3.5)	30.7 (2.8) [a]	30.4 (2.3) [a]
Waist circumference (cm)	120.1 (9.0)	109.5 (7.8) [a]	108.0 (7.9) [a]
HbA1c (mmol/mol)	67.6 (12.3)	49.7 (9.9) [a]	59.7 (17.3) [a,b]
FPG (mmol/L)	11.98 (3.22)	8.69 (2.65) [a]	10.40 (4.05) [a,b]
Fasting plasma insulin (mU/L)	23.9 (11.8)	17.5 (9.8)	13.9 (6.0)
SBP (mmHg)	136.7 (14.0)	126.0 (14.7) [a]	131.0 (9.9)
DBP (mmHg)	79.8 (7.1)	74.7 (7.2)	83.2 (8.8) [b]
Total cholesterol (mmol/L)	4.03 (0.56)	3.93 (0.74)	4.19 (0.72)
LDL-cholesterol (mmol/L)	2.02 (1.01)	2.03 (0.64)	2.14 (0.83)
HDL-cholesterol (mmol/L)	1.00 (0.19)	1.12 (0.37) [a]	1.15 (0.28) [a]
Triglycerides (mmol/L)	2.81 (1.51)	2.07 (1.36) [a]	2.38 (1.54) [a]

Data are means ± standard deviations (SDs); a = significantly different from baseline at $p < 0.05$; b = significant difference between three months and six months at $p < 0.05$.

3.1.1. Changes in Medication Use During the Intervention

At baseline, two participants used insulin, SU derivatives and metformin, one used insulin, a GLP-1 agonist and metformin, three used insulin and metformin, five participants used SU derivatives and metformin, three used only metformin, and one participant was about to start

metformin. All participants that were on insulin treatment and/or SU derivatives at the start of the intervention period stopped using this medication during the entire six-month period of the intervention. Out of 14 subjects using metformin at baseline, three subjects used a decreased dosage and one participant stopped using metformin after three months of intervention. At six months of intervention, an additional three participants used a lower dosage, and two out of three participants who had a decreased dosage at three months completely stopped using metformin at six months, whereas the third person returned to the baseline metformin dosage. Two participants were using GLP-1 agonists at three months and at six months of intervention.

In terms of medication for comorbidities, out of 11 participants using blood pressure-lowering medication at baseline, four had a decreased dosage and two completely stopped using this medication at six months of intervention. Furthermore, out of 12 participants using lipid-lowering medication at baseline, five had a decreased dosage and one completely stopped using this medication at six months of intervention.

3.1.2. Changes in Metabolic Phenotype During the Intervention

Diabetyping was done using the results of the OGTT. At baseline, 12 participants had impaired BCF combined with hepatic IR (IB-HIR), and one subject had isolated impaired BCF (IB). For two participants, the T2D subtype could not be determined at baseline due to missing data. After three months of intervention, one participant had IB, seven participants had IB-HIR, and seven participants had impaired BCF and muscle and hepatic IR (combined IR; IB-CIR). After six months of intervention, 10 participants had IB-HIR and five participants had IB-CIR (Figure 1).

After three months of intervention, glucose at t = 0 ($p < 0.001$), glucose at t = 120 ($p < 0.001$), HOMA-IR ($p = 0.002$), HIRI ($p = 0.006$), Matsuda index ($p = 0.042$), and disposition index ($p < 0.001$) improved compared to baseline (Table 4). This improvement was maintained after six months of intervention. The Matsuda index improved further between three and six months of intervention ($p = 0.048$). Insulin at t = 0 ($p = 0.002$) and t = 120 ($p = 0.007$) were significantly lower after six months of intervention compared to baseline and compared to three months of intervention for insulin at t = 120 ($p = 0.001$). The MISI increased after three months of intervention ($p = 0.011$) but decreased after six months of intervention ($p = 0.012$) compared to baseline.

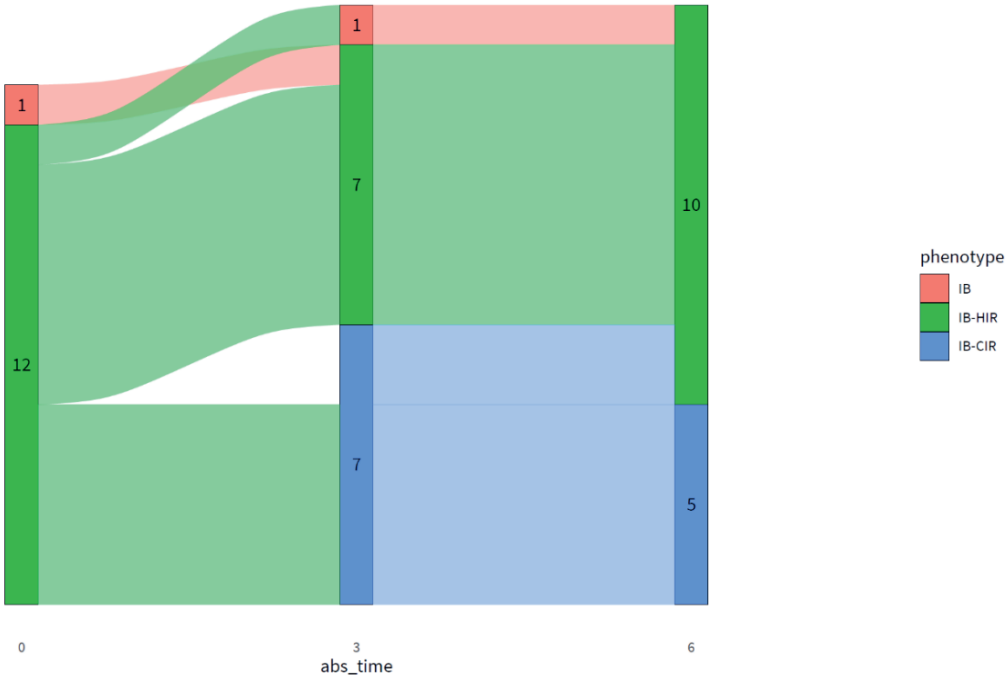

Figure 1. *Flow diagram showing the diabetic subtypes at baseline, three months, and six months; subtype from two participants could not be calculated at baseline due to missing data. IB = impaired beta cell function; HIR = hepatic insulin resistance; CIR = combined (liver and muscle) insulin resistance. Abs_time: time of intervention (months). Numbers within the figure indicate the number of participants with that subtype at each time of intervention.*

3.1.3. Diabetes Remission and Diabetes Reversal

Figure 2 shows the number of participants who were in reversal or remission after three and six months of intervention. At baseline, all participants were classified as having T2D. After three months of intervention, four participants achieved T2D reversal and two achieved T2D remission. After six months of intervention, three out of four participants who were in T2D reversal after three months were still in reversal, and one participant relapsed to T2D. The two participants who were in remission after three months maintained this T2D remission at six months.

***Table 4**. Changes in oral glucose tolerance test (OGTT) response between baseline, three months, and six months of intervention.*

Variable	Mean (SD)		
	Baseline	**Three Months**	**Six Months**
Glucose (mmol/L) at t = 0 min	12.00 (3.22)	8.69 (2.65) [a]	10.40 (4.05) [a,b]
Glucose (mmol/L) at t = 120 min	21.40 (4.46)	18.20 (4.91) [a]	18.80 (6.01) [a]
Insulin (mU/L) at t = 0 min	23.9 (11.8)	17.5 (9.8)	13.9 (6.0) [a]
Insulin (mU/L) at t = 120 min	51.0 (38.3)	58.6 (41.9)	35.8 (27.6) [a,b]
HOMA-IR	12.80 (7.18)	6.86 (5.08) [a]	6.44 (4.38) [a]
HIRI	5180 (2910)	2720 (2060) [a]	2610 (1770) [a]
MISI	−3.04 (1.59)	−2.03 (2.44) [a]	−3.26 (3.02) [b]
Matsuda index	1.60 (1.25)	2.00 (0.82) [a]	2.57 (1.05) [a,b]
Disposition index	0.21 (0.22)	0.46 (0.29) [a]	0.35 (0.24) [a]

Data are means ± standard deviations (SDs); a = significantly different from baseline at $p < 0.05$; b = significant difference between three months and six months at $p < 0.05$.

3.2. Metabolic Phenotypes of Three Study Participants

For three study participants, in-depth details of their metabolic phenotypes are presented to show their personal routes: one who achieved remission, one who achieved reversal, and one who achieved neither reversal nor remission. All three selected participants were compliant with the given lifestyle advice.

3.2.1. Metabolic Phenotype of a Participant Achieving T2D Remission

Participant A, a 62-year-old female with a T2D duration of 18 years and using metformin, achieved diabetes remission after three months, and maintained this after six months of intervention. At baseline, this participant had a body weight of 105 kg and a waist circumference of 120 cm. This participant managed to lose weight and had a decreased waist circumference after three (~13 kg and 15 cm, respectively) and six months (~18 kg and 19 cm, respectively). At the start of the intervention (i.e., after baseline), this participant stopped taking metformin. HbA1c levels were lower after three and six months compared to baseline (Table 5). Blood glucose levels (all time points) decreased after three and six months of intervention compared to baseline (Figure 3A). Fasting insulin levels decreased after three and six months of intervention, and postprandial insulin levels decreased after six months of intervention (Figure 3B). All T2D indices, except for disposition index, improved during the intervention period (Table 5). Despite the improved indices, the T2D subtype at all three time points was IB-HIR, meaning impaired BCF with hepatic IR and no muscle IR.

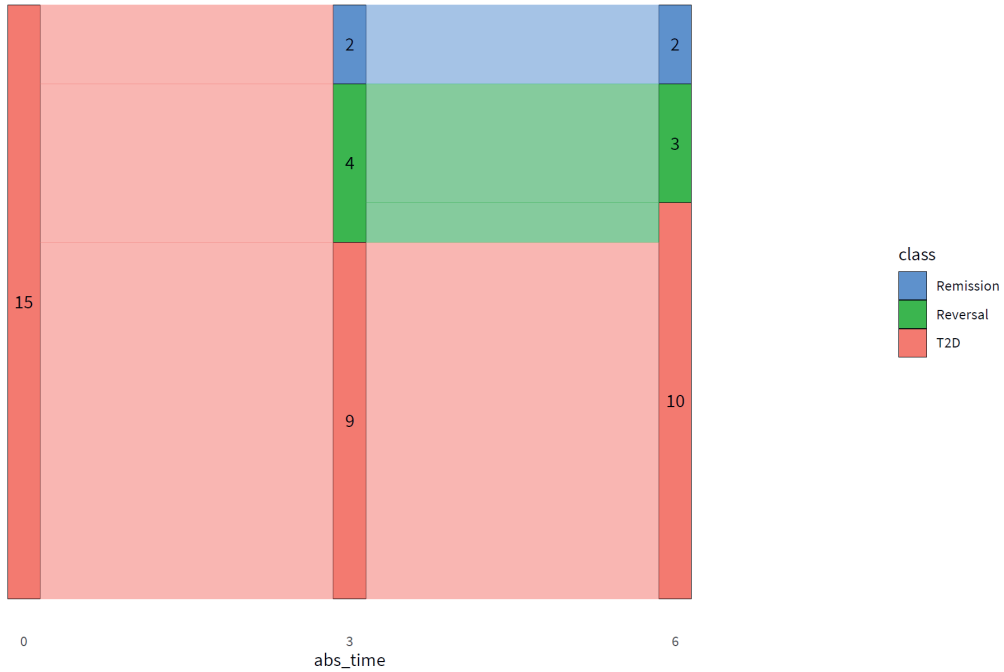

Figure 2. *The number of participants who were classified as having T2D, in reversal, or in remission of T2D after three months and six months of intervention compared to baseline. Remission was defined as FPG ≤ 6.9 mmol/L and HbA1c < 48 mmol/mol and no medication use. T2D reversal was defined as attaining target values for HbA1c (≤ 53 mmol/mol) and fasting glucose (< 8.0 mmol/L) (Barents et al., 2018) with reduced medication (taking fewer types or a lower dose of glucose-lowering medication at three or six months compared to the start of the trial) or attaining normalized HbA1c (< 48 mmol/mol) and fasting glucose (≤ 6.9 mmol/L) with equal medication at three or six months compared to the start of the trial. Abs_time: time of intervention (months). Numbers within the figure indicate the number of participants with that classification at each time of intervention.*

Table 5. *HbA1c and T2D indices derived from OGTT for participant A at baseline and after three months and six months of intervention.*

	Baseline	**Three months**	**Six months**
HbA1c	47	32	36
Matsuda index	1.10	2.06	2.22
Disposition index	0.15	0.28	0.27
MISI	−2.13	−8.00	−10.31
HIRI	4779	2393	2343
HOMA-IR	11.8	5.91	5.78

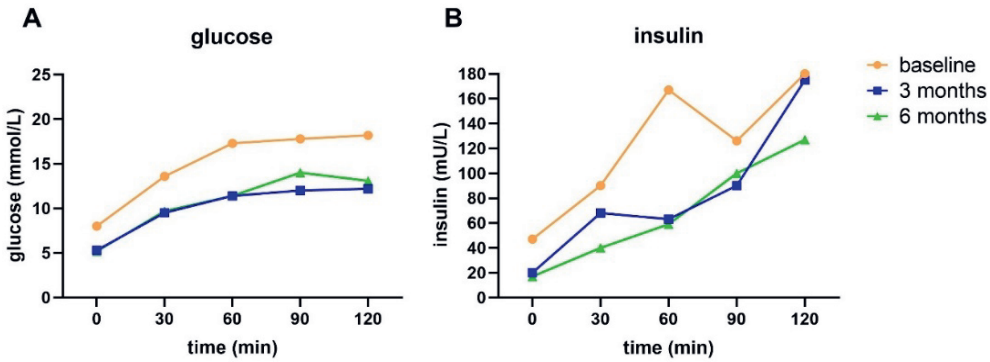

Figure 3. *Glucose (A) and insulin (B) response to an OGTT at baseline and after three and six months of intervention for participant A.*

3.2.2. Metabolic Phenotype of a Participant Achieving T2D Reversal

Participant B, a 61-year-old female with a T2D duration of 11 years and taking metformin, did not achieve diabetes remission nor reversal after three months, but did achieve reversal after six months of intervention. At baseline, this participant had a weight of 105 kg and a waist circumference of 128 cm. This participant managed to lose weight and had a decreased waist circumference after three (~10 kg and 12 cm, respectively) and six months (~18 kg and 17 cm, respectively). After six months, the participant could reduce the dosage of metformin. HbA1c levels were lower after three and six months compared to baseline (Table 6). Blood glucose levels (all time points) were lower after three months, and postprandial glucose was further lowered from three to six months (Figure 4A).

Table 6. *HbA1c and T2D indices derived from OGTT for participant B at baseline and after three months and six months of intervention.*

	Baseline	**Three months**	**Six months**
HbA1c	61	39	39
Matsuda index	1.07	1.64	1.85
Disposition index	0.03	0.10	0.03
MISI	−3.84	−1.24	−5.83
HIRI	6217	3523	3431
HOMA-IR	15.35	8.70	8.47

Insulin levels (all time points) remained relatively stable between baseline and three months of intervention but were lower after six months of intervention (Figure 4B). Matsuda index, HIRI, and HOMA-IR improved, but were not normalized after six months of intervention (Table 6). Disposition index remained relatively stable, whereas MISI worsened from baseline to three months, but improved from three to six months. The T2D subtype was IB-HIR at all three time points, meaning hepatic IR and impaired BCF and no muscle IR.

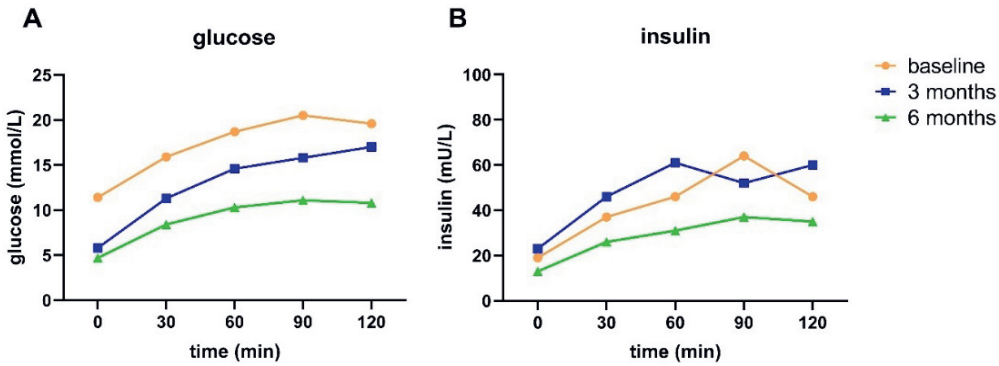

Figure 4*. Glucose (A) and insulin (B) response to an OGTT at baseline and after three and six months of intervention for participant B.*

3.2.3. Metabolic Phenotype of a Participant Achieving Neither T2D Reversal nor Remission

Participant C, a 65-year-old male with a T2D duration of 24 years and taking metformin and SU derivatives, did not achieve diabetes remission or reversal after three months or six months of intervention. At baseline, this participant had a weight of 124 kg and a waist circumference of 137 cm. This participant managed to lose weight (~10 kg) and had a decreased waist circumference (~7 cm) after three and six months, albeit to a lesser extent than participants A and B. At the start of the intervention (i.e., after baseline), this participant stopped taking SU derivatives. Blood glucose levels (all time points) and HbA1c were lower at three and six months compared to baseline (Table 7 and Figure 5A).

Table 7. *HbA1c and T2D indices derived from an OGTT for participant C at baseline and after three months and six months of intervention.*

	Baseline	**Three months**	**Six months**
HbA1c	72	54	58
Matsuda index	2.86	4.39	4.32
Disposition Index	0.64	0.80	0.40
MISI	−5.52	−2.44	−3.34
HIRI	1586	808	1090
HOMA-IR	3.92	2.00	2.69

Fasting insulin levels decreased after three and six months of intervention, but the insulin response to the OGTT remained relatively stable (Figure 5B). Matsuda index and HIRI improved during the entire intervention period, as well as HOMA-IR, especially during the first three months of intervention (Table 7). Disposition index remained relatively stable. At baseline, the T2D subtype was IB-HIR, meaning hepatic IR and impaired BCF and no muscle IR. The improvement in HIRI after three months was reflected by the shift in subtype from

IB-HIR to IB, indicating that hepatic IR was reversed. At six months, this participant reverted to IB-HIR.

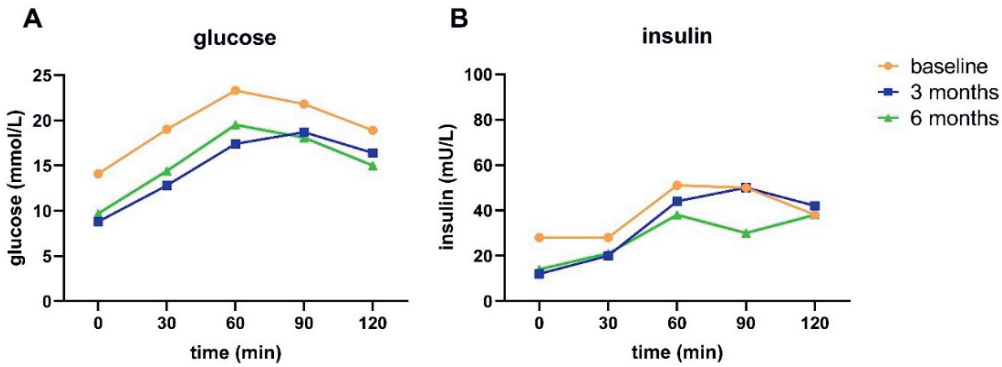

***Figure 5**. Glucose (A) and insulin (B) response to an OGTT at baseline and after three and six months of intervention for participant C.*

4. DISCUSSION

The DLI resulted in remission in two and reversal in three out of 15 participants after six months. Additionally, the DLI resulted in improved pathophysiology and glucose metabolism in people with advanced T2D, reflected by an improved fasting and 2h plasma glucose and insulin, HOMA-IR, disposition index, HIRI, and MISI. With an average weight loss of ~11 kg and an average decrease in waist circumference of ~12 cm in our study population, the improvements in glucose metabolism are probably at least partly driven by weight loss [40].

Even though most participants achieved substantial weight loss, remission was achieved by two participants, or 13% of the study population. Higher remission numbers have been reported previously [41,42], although some caution should be taken in directly comparing remission numbers across studies due to differences in the definitions used for T2D remission [18]. Additionally, our study population is relatively small compared to some landmark trials. For illustrative purposes, we compare the % remission achieved in our study with other studies. The DiRECT, U-TURN, and Look AHEAD trials achieved remission in 46, 37, and 11.5% of the study population, respectively [41–44]. Differences compared to our study were shorter disease duration, larger study population, and longer intensive intervention period. It has been shown previously that the chance of achieving (partial) T2D remission is higher among persons with a shorter disease duration, lower age, and lower baseline HbA1c, who are not using insulin, and when pharmacological treatment is not yet initiated [43,44]. In another primary care study with recently diagnosed T2D, 35% of the participants normalized their BCF after the lifestyle intervention [45]. This confirms that achieving remission is especially effective in the early stages of T2D [14]. Additionally, all participants in our study suffered from comorbidities and met the criteria for metabolic syndrome according to the

International Diabetes Federation [39]. These comorbidities may influence intervention effectiveness. Furthermore, the intensity of lifestyle treatment was recently identified as a factor influencing the chance of remission, with higher remission rates in studies using very low-calorie and longer-term diets compared to studies using moderate calorie restriction [18]. In our study, participants followed a very low-calorie diet for only one week, followed by a six-week low-carb diet and thereafter a gradual reintroduction to a Mediterranean diet. The difference in lifestyle intervention intensity may partly explain the difference in remission rates between the studies, although "the introduction of short-term major caloric reduction with total diet replacement and a stepped food re-introduction" has been acknowledged as an effective method for diabetes remission [14].

Even in studies that apply longer-term intensive lifestyle interventions, non-responders are identified [46], with non-response mainly ascribed to the lowered ability of beta cells to recover [47]. The ability to achieve remission during an intervention consisting of a very low-calorie diet [41,48] or intensive physical training depended on the patient's pancreas capacity [42,46]. In our study, all participants had an impaired BCF at baseline, as determined by the diabetyping algorithm. One participant had isolated impaired BCF, and 12 had impaired BCF combined with HIR. After three and six months of intervention, BCF only slightly improved as measured by an improved disposition index, while all other indices (except MISI) showed a much larger improvement. The lowered ability of BCF to recover was previously linked to disease duration [47]. Additionally, it has been shown previously that BCF declines with age [49,50]. Despite the impaired BCF and higher age in our study population, two participants were able to achieve T2D remission, and three were able to achieve T2D reversal. From the data of participant A and B, it can be observed that, even though remission or reversal has been achieved, all indices except MISI were still impaired at three and six months of intervention compared to a healthy population [31]. This indicates that even though reversal or remission has been achieved, insulin sensitivity and BCF were not fully recovered.

Our data show that HbA1c and FPG do not provide a complete picture of the pathophysiology in people with T2D, as underlying pathophysiology—including impaired BCF and insulin resistance—can still be present in the case of normalized HbA1c and FPG and cessation of medication. Thus, achieving remission cannot be considered as a cure of T2D [43]. We therefore suggest applying an extended OGTT to get a better understanding of the (remaining) underlying pathophysiology in people with T2D and those who are in remission. Especially in the case of remaining underlying pathophysiology, bodyweight regain, or unhealthy lifestyle may lead to relapse [48], implying the need for long-term adherence to a healthy lifestyle and continued monitoring of people in remission of T2D [14]. In our study, HbA1c and FPG deteriorated from three to six months of intervention, which could be linked to a lowered compliance to the lifestyle intervention reported by participants.

In a general diabetes population, the rate of (partial) T2D remission is extremely low [44]. In fact, most people with T2D show progression of the disease with rising FPG and HbA1c and

increasing medication use over time [51–53]. In that respect, in a clinical setting, halting disease progression or reversing the disease could already be considered clinically meaningful. In our study, we therefore introduced T2D reversal, meaning that a patient requires less medication for attaining target values of HbA1c and FPG or attaining normalized HbA1c and FPG values on unchanged medication. On top of the two participants achieving T2D remission, four participants achieved T2D reversal at three months, of which three were able to maintain this up to six months of intervention. Interestingly, all participants were able to lower their medication use while maintaining or lowering HbA1c and FPG values. In addition, participant C did not meet the criteria for achieving remission or reversal but was able to attain substantially lower glucose and HbA1c levels while using less medication, which can be considered clinically relevant. As medication can induce side effects and patients experience a higher treatment burden when using multiple medications, especially insulin, a reduction in medication use can be considered a major advantage of lifestyle treatment [52,54,55].

Besides improvements in glucose metabolism and body weight, improvements in overall health status were observed with improved SBP (at three months only), HDL cholesterol, and triglycerides, while overall medication use for these comorbidities was decreased. So, on top of improving glucose metabolism, the lifestyle intervention also had beneficial effects in addressing the metabolic syndrome in our study population. Therefore, when assessing the effects of lifestyle interventions in T2D, overall health effects, including the impact on body weight, blood pressure, blood lipids, and medication use, should be considered.

The strengths of our study include that the study was conducted in a primary care setting, i.e., a real-life setting. Participants showed good compliance to the advice, possibly due to the intensive and personal approach of the health care providers, and close collaboration between the different health care providers (dietician, pharmacist, practice nurse, GP). We showed that the Diabetyping Lifestyle Intervention is feasible in a Dutch primary care center.

A few limitations need to be discussed. Firstly, the study population was small, as this was the maximum number of participants that the healthcare professionals of the involved primary care center could intensively coach. Secondly, there was little diversity in terms of the T2D subtypes in our study population. This may be an artefact of current T2D diagnosis in the Netherlands. As 2h glucose is not measured as part of usual care, people with isolated impaired glucose tolerance (IGT), which often coincides with muscle IR, are easily missed [56]. Additionally, our study population had long-standing T2D (13.4 ± 5.2 yrs), which may explain the high prevalence of impaired BCF.

Thirdly, medication was stopped at 20:00 the day before the OGTT. This was possibly not long enough, as especially long-acting insulin may still have influenced the blood glucose and insulin values. This was especially the case for the OGTT performed at baseline, since all participants stopped using insulin during the intervention period. Additionally, the OGTT

was not performed after three days of unrestricted diet with at least 150 g of carbohydrates as recommended by the WHO [25], but guidelines from standard clinical practice were followed, as the DLI was implemented as part of regular primary care. These clinical practice guidelines for the OGTT only dictate fasting of at least 10 h prior to the test. Carb load prior to the OGTT may therefore have influenced the results for participants on the low-carb diet (75 g per day) at three or six months. However, in our study, not only glucose, but also insulin is measured, allowing for interpretation of the interaction between glucose and insulin, which may be less sensitive to prior carbohydrate loading.

5. CONCLUSIONS

In our study, we show that remission and reversal can be achieved by lifestyle treatment in a small cohort of people with long-standing T2D. The DLI resulted in body weight loss, improved pathophysiology, and improved metabolic health. In our study, achieving diabetes remission or reversal, in terms of normalized glucose and HbA1c and cessation or reduction of medication use, coincided with remaining underlying pathology, indicating that diabetes remission does not equalize a cure. This is important patient information for the subsequent lifestyle therapy. Therefore, we suggest that even people who fully achieve remission should remain under supervision of a healthcare professional and may need to adhere to a specific lifestyle regimen in the long term. On the other hand, even for people who do not achieve remission or reversal, the overall changes in health status and medication use that can be achieved via lifestyle treatment could still be clinically meaningful.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

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6

DIGITAL BIOMARKERS FOR PERSONALIZED NUTRITION: PREDICTING MEAL MOMENTS AND INTERSTITIAL GLUCOSE WITH NON-INVASIVE, WEARABLE TECHNOLOGIES

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ABSTRACT

Digital health technologies may support the management and prevention of disease through personalized lifestyle interventions. Wearables and smartphones are increasingly used to continuously monitor health and disease in everyday life, targeting health maintenance. Here, we aim to demonstrate the potential of wearables and smartphones to (1) detect eating moments and (2) predict and explain individual glucose levels in healthy individuals, ultimately supporting health self-management. Twenty-four individuals collected continuous data from interstitial glucose monitoring, food logging, activity, and sleep tracking over 14 days. We demonstrated the use of continuous glucose monitoring and activity tracking in detecting eating moments with a prediction model showing an accuracy of 92.3% (87.2–96%) and 76.8% (74.3–81.2%) in the training and test datasets, respectively. Additionally, we showed the prediction of glucose peaks from food logging, activity tracking, and sleep monitoring with an overall mean absolute error of 0.32 (+/- 0.04) mmol/L for the training data and 0.62 (+/- 0.15) mmol/L for the test data. With Shapley additive explanations, the personal lifestyle elements important for predicting individual glucose peaks were identified, providing a basis for personalized lifestyle advice. Pending further validation of these digital biomarkers, they show promise in supporting the prevention and management of type 2 diabetes through personalized lifestyle recommendations.

1. INTRODUCTION

Type 2 diabetes (T2D) is a top-10 leading cause of disability-adjusted life years (DALYs) in the last decade, and it is anticipated to affect more than 7% of the world population by 2030 [1,2]. Beyond pharmacological therapy, lifestyle medicine targeting insulin resistance as the root cause of T2D is becoming evident now in remitting, reversing, or preventing the disease [3–8]. Digital technologies that support individuals in changing and monitoring their lifestyles, such as dietary behavior, physical activity, sleep, and stress, are promising for supporting lifestyle medicine [9].

The implementation of lifestyle medicine with sustained lifestyle behavior change necessitates a personalized approach, including personalized diagnosis and diet, physical activity and stress management, self-empowerment, motivation, participation, and health literacy [9]. Increasing evidence shows that T2D subgroups exist with different underlying etiology, demonstrating a differential response to lifestyle interventions [10–14]. Additionally, several studies have demonstrated the potential of a personalized nutrition approach to improve health in a (relatively) healthy population [15–19]. Full remission into a healthy glucose metabolism through lifestyle medicine is well achievable, especially in the early phase preceding the disease. Multiple studies, indeed, have shown that lifestyle medicine is only successful in achieving T2D remission in a pre- or less advanced stage of the disease, but often fails in persons who have a more advanced, irreversible stage of T2D, especially those with β-cell dysfunction or combined tissue insulin resistance [20–22]. Therefore, early diagnosis and intervention are essential for reducing the societal burden of T2D. In most of these studies, an extensive baseline assessment, including invasive measurements, such as blood, saliva, or feces collection and postprandial biomarker evaluation with challenge testing, was used to provide personalized dietary recommendations. Challenge tests, such as a mixed-meal challenge test or an oral glucose tolerance test (OGTT), offer insights into dynamical biomarker responses to a standardized meal, as opposed to solely looking at overnight fasting biomarkers [23]. This allows for earlier detection of a pre-stage of the disease or derailment of health. T2D develops gradually, whereas prediabetes can exist for years with increased levels of insulin but relatively normal levels of overnight fasting glucose [24].

Wearable technologies, including smartphones and smartwatches, are increasingly utilized in the healthcare domain for the development of so-called digital biomarkers [25–27]. This novel type of biomarker is characterized by being measured non-invasively, continuously, and under real-world conditions using digital technology, allowing for a more holistic and personal insight into someone's health. Therefore, digital biomarkers enable accessible health and behavioral feedback to the user and are particularly suited for driving the healthcare transition towards prevention, empowering people in the self-management of health and disease [28]. Additionally, continuous, non-invasive, or minimally invasive measurements may allow for the measurement of subtle health derailments by evaluating the responses or

resilience towards daily challenges or perturbations, thereby allowing for such early diagnosis [28]. Continuous glucose monitoring (CGM), for example, is used to define so-called 'glucotypes' based on glucose patterns, which are associated with clinical biomarkers of glucose dysregulation [29]. Furthermore, digital biomarkers can provide users with more frequent and detailed contextual information and continuously update personal lifestyle recommendations. Indeed, postprandial glucose responses to meals are highly personal and depend on a person's genetic makeup and clinical factors (e.g., BMI, microbiome, lipid levels), and also on the context of the meal, and include factors such as sleep, physical activity, and composition of previous meals [30,31]. These contextual factors, which strongly influence glucose homeostasis, are difficult to manage in a traditional healthcare setting due to their limited ability to capture daily life conditions. Recently, it was shown that interstitial glucose levels can be predicted from continuous contextual data, including those on diet and physical activity, in persons with prediabetes under real-world conditions [32]. High-quality contextual data collection is essential for this. While, for sleep and activity tracking, wearable technologies are becoming more reliable for passive monitoring, meal tracking requires active, continuous logging from the user, impacting this essential data quality. Food frequency questionnaires, 24 h recall interviews, or food diaries are the most common methods for monitoring dietary behavior and estimate dietary intake, although these methods are susceptible to misreporting [33,34]. Recently, CGM-based meal-detection algorithms were proposed for people with type 1 diabetes (T1D), showing the potential for CGM to support dietary intake monitoring [35,36]. To our knowledge, this has not been presented for healthy people, persons with prediabetes, or persons with T2D. Altogether, there is a need for high-quality contextual data from everyday life that can be linked to glucose dynamics to support health self-management for the prevention of T2D.

The current study set out to demonstrate a proof of principle for detecting eating moments with CGM, as well as predicting and explaining glucose levels based on contextual factors, such as sleep, activity, and diet in a personalized manner, ultimately supporting health self-management and prevention of T2D. Therefore, we performed an observational study with 24 healthy adult volunteers who conducted continuous self-monitoring for two weeks in a real-life setting. The volunteers wore a CGM device for glucose monitoring and a smartwatch for monitoring physical activity and sleep and logged their food intake via a mobile food diary app. The study evaluated how well the probability of having an eating moment can be predicted based on continuously measured glucose, sleep, and activity data. Personalized insight into eating moments can form the basis for personalized advice on the timing of eating. In addition, passive detection of eating moments has the potential to notify individuals to fill out the food diary and to improve compliance with data collection. Additionally, personal glucose prediction models were created to model the effects of physical activity, dietary intake, and sleep on individual glucose levels. How well the glucose levels can be predicted based on personal lifestyle behavior, including dietary intake, sleep, and activity

data, was evaluated since personalized insights into the effects of lifestyle behavior on glucose levels can support an individual in keeping glucose levels within a healthy range.

2. MATERIALS AND METHODS

2.1. Study Design and Data Collection

Twenty-four healthy volunteers with an affinity for nutrition and health research were included in this observational pilot study. Participants were eligible for study participation if they were aged 20–65, owned a smartphone, and had a finger-prick glucose value < 7.8 mmol/l after eight hours of fasting during screening to exclude for unknown type 2 diabetes. Exclusion criteria were having type 2 diabetes, body mass index > 30 kg/m^2, and conditions that would not allow the use of a continuous glucose monitoring system, such as a skin allergy or eczema. All participants gave written, informed consent.

At inclusion, participants were equipped with self-monitoring devices, installed the custom-built Android- and iOS-compatible *HowAmI* app (TNO, Zeist, The Netherlands) on their smartphones, and were instructed in the use of all devices and apps. The study consisted of 14 days of self-monitoring in a real-life setting. The self-monitoring devices were the Abbott FreeStyle® Libre™ Pro (Abbott GmbH & Co, Wiesbaden, Germany) continuous glucose monitoring (CGM) device and the Philips Elan wristband (Koninklijke Philips N.V., Eindhoven, Netherlands). The factory calibrated CGM device was worn on the upper arm and measured subcutaneous interstitial glucose concentrations every fifteen minutes. Participants were blinded to their glucose values. Glucose data were stored on the CGM devices, which were collected at the end of the study. Glucose measurements from the first day were excluded to allow for the stabilization of the sensor. The Elan wristband collected data via a raw green spectrum photoplethysmogram (PPG) sensor and accelerometer. Data were regularly offloaded by participants using ElanControl software (Koninklijke Philips N.V., Eindhoven, Netherlands) and transferred to Philips after the study. Proprietary algorithms were used to translate the raw data into sleep, energy expenditure, ACN, and heart rate. The *HowAmI* app was used for collecting food intake. The app was custom-built to provide the functionality to record the exact date and time of the recorded meals. The *HowAmI* app uses the *MyFatSecret* food database and back-end (Secret Industries Pty Ltd., Victoria, Australia) to record food intake and connects to a custom, parallel back-end database to record the time stamp for each meal. This same database was used to collect and store data from the continuous glucose monitor. Helpdesk support was available throughout the study. Participants could follow their regular lifestyle during the study. The study protocol was approved by the Medical Ethics Committee Brabant (NL68969.028.19). The study was performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Netherlands Trial Register: NL7117.

2.2. Data Preprocessing and Feature Engineering

After data collection, all subsequent data processing, analysis, and visualization were performed using R, version 4.1.2. We used packages ggplot 3.3.5, xgboost 1.5.0.2, caret 6.0–90, pracma 2.3.8, and treeshap 0.1.1 [63–67]. Figure 1 provides a schematic overview of the different steps taken in data preprocessing, model fitting, and model analysis, while details are provided below.

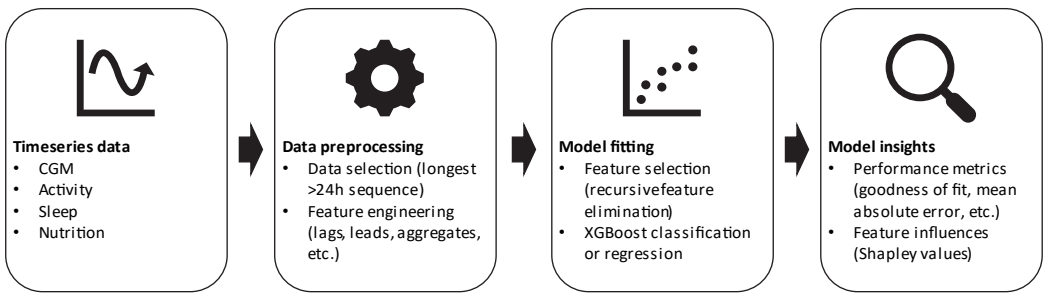

Figure 1. *Schematic overview of the steps taken in model development and evaluation of the time-series data. Two models were developed, both following this workflow in a specific manner. The model predicting eating moments takes the CGM and activity time-series data as input to use XGBoost classification to classify whether there is an eating moment or not. The other model uses activity, sleep, and nutrition data as input to predict glucose levels, while, for individual glucose peaks, Shapley values are calculated to indicate the individual importance of activity, sleep, and/or nutrition in explaining these peaks. Further details are provided in the methods sections 'Data preprocessing and feature engineering' and 'XGboost for predicting eating moments and glucose'.*

We created an appropriate dataset for the detection of meals in a multi-step process consisting of data aggregation and feature engineering. Several engineered features were created from continuous glucose sensor data that matched the sampling interval of the glucose sensor. We created lag, lead, the difference of the lead (1st to 6th order), the difference of the log lead (1st to 6th order), lagged difference of the lead (1st to 6th order), standard deviation and mean of the lead up to 90 min, standard deviation and mean of the lag up to the 90 min, standard deviation and mean from a 90 min lag to a 90 min lead, relative standard deviations of the 90 min lead and lag, the ratio between the standard deviation of the lead and the lag, and the ratio between the 90 min lead and lag maximum and minimum values. No other modalities were used in the meal detection dataset. The target variable was given as a classification label, where the positive class denotes that food was taken at that respective time point, and the negative class denotes that no food was taken. A time point was of the positive class if the meal contained any carbohydrates; the time points immediately preceding and following food intake were also considered to be of the positive class to account for inaccuracies in diary annotation and the time it took to consume the food.

A similar approach was taken to create a suitable dataset for the prediction of glucose. Data were first aggregated to deal with varying sampling intervals across the different modalities.

The items of any meal that were eaten within 15 min were combined to form a single meal. For each meal, total calories, as well as calories from fat, protein, and carbohydrates, were calculated. From this, the fractions of calories from fat, protein, and carbohydrates were also derived. Additionally, energy expenditure, acceleration (movement), and heart rate features collected from the Elan wristband were aligned to the collection interval of the continuous glucose sensor (once every 15 min) and then aggregated to match the frequency of the glucose measurements before being joined. Sleep and sleep stage information were subsequently joined so that each glucose value was associated with sleep feature values from the closest preceding period of sleep, but no more than 28 h earlier.

Subsequently, we created new features from all aggregated and joined data (except sleep-related data) by averaging the values for all features over rolling periods of 30, 60, and 90 min as well as 2, 3, 8, and 24 h. In the case of caloric intake, energy expenditure, and activity, these features were created by taking the rolling sum instead of the rolling average.

The final datasets were created from this data by selecting the longest stretch of uninterrupted data that was available from every included participant with a minimal stretch of 24 h. For this purpose, we defined 'uninterrupted data' as periods where data from all modalities were available without a break in the glucose sensor measurements and no break in the activity or food intake measurements. In addition, the total length of combined stretches per participant needed to exceed 7 days to allow sufficient data for training and test sets.

The training set for the glucose prediction model contained all available data for each participant apart from those from the last 3 days; these were kept separate for the testing set. The training dataset for the meal detection model was more limited; we used the first 4 days of data for each participant for training purposes and kept a subsequent 3-day period as the training set. The training dataset for the meal detection model was kept intentionally smaller to imitate a practical situation where only limited data can be obtained because of the participant burden of keeping a food intake diary.

In the case of both models, the test dataset was used to estimate model generalizability but not for any other purposes.

2.3. XGboost for Predicting Eating Moments and Glucose

For both models, we used recursive feature elimination (RFE) with 10-fold cross-validation to obtain the smallest set of features that would still perform similarly to the full feature set. This step was undertaken to simplify the model for easier interpretation and reduce overfitting. In this procedure, we used xgboost as the underlying model to drive feature selection; *gain*, as a measure of improvement in accuracy, was used to rank feature importance during RFE [64]. A fixed number of rounds (100) was used at every iteration of the procedure; no hyperparameter tuning was performed. The smallest set of features where

model performance was within 10% of the best-performing set was selected for use in the final prediction model.

For the final glucose prediction model, the model hyperparameters were tuned by minimizing the mean absolute error using random search with 10-fold cross-validation. The target variable was the log-transformed glucose value. The hyperparameter tuning procedure for the meal detection model minimized the classification error using grid search with 10-fold cross-validation. Grid search was chosen over random search because of the propensity for overfitting and its reduced computation time because of a smaller amount of training data compared to the glucose prediction model.

For the glucose prediction model, Shapley values were calculated for all data points in the training dataset by using the implementation of the algorithm described in Lundberg et al. [62] and provided by the *treeshap* package. This algorithm was defined using a mathematical game theoretic approach that is explained in detail by Lundberg et al. [62]. These Shapley values provided information for each predicted value about the influence of each model feature in making that prediction. We used the Shapley values to determine overall feature importance (Supplementary Table S1) by taking the mean absolute Shapley value for each feature for all predictions. Furthermore, we used the Shapley values to determine the feature influence in the prediction of peak glucose levels. Using the *findpeaks* algorithm of the *pracma* package, we identified peaks for all subjects where the glucose value was higher than at least the $IQR + Q_3$ for that subject. This led to a varying number of identified peaks for each of the subjects; for further analysis, we included only those subjects with 10 or more identified peaks.

3. RESULTS

3.1. Baseline Characteristics and Dataset Characteristics

A total of 24 individuals participated in the study. The study participants were, on average, 39 +/− 12 years old with an average body mass index (BMI) of 22 +/− 9.4 kg/m^2. Of the 24 participants, 17 participants were female (71%). All individuals had non-fasting blood glucose in the normal range below 7.8 mmol/L during screening, which excluded people with unknown diabetes. A minimal length of uninterrupted data periods for 24 h from all continuous data sources was selected for all participants to guarantee sufficient data quality. Additionally, at least three days of test data and three days of training data were required to ensure sufficient power to perform the analysis. Applying these two criteria resulted in a dataset with 11 individuals with 4–11 days of training data and three days of testing data that was selected for further analysis (Figure 2).

Figure 2. *Overview of data availability for physical activity (green), sleep (yellow), dietary intake (pink), and interstitial glucose (purple). Data selected for further analysis are marked with an arrow.*

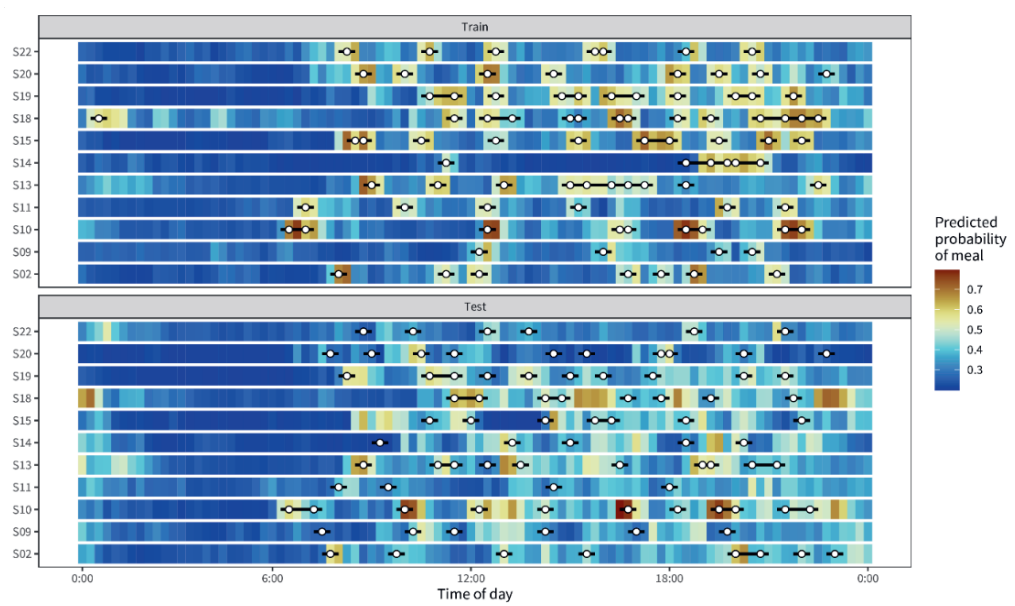

Figure 3. *Predicted probability of an eating moment in blue against the indicated eating moments by the subjects (white dots). Probabilities were calculated for segments of 30 min; 15 min before and 15 min after an eating moment, indicated by the black bars around the white dots.*

3.2. Detecting Eating Moments Based on Interstitial Glucose Levels

Detecting eating moments can support food logging, for example, through AI-driven notifications, thereby reducing the risk of erroneous reporting. We developed an extreme gradient boosting machine model to predict the probability of having an eating moment in healthy individuals. Eating moments were predicted in segments of 30 min based on continuously collected interstitial glucose, sleep, and activity data over three days per participant. After model training, accuracy, specificity, and sensitivity were calculated using a hold-out test dataset. The final model showed an accuracy, specificity, and sensitivity of 92.3% (87.2–96%), 98.9% (97–100%), and 90.8% (86.4–94.9%), respectively. The accuracy, specificity, and sensitivity in the test dataset of another three days per individual were 76.8% (74.3–81.2%), 60.3% (33.3–82.6%), and 78.4% (74.3–84.1%), respectively. Figure 3 visualizes the predicted probability in segments of 30 min against the observed eating moment for both the training and the test dataset, confirming the high level of accuracy in the training dataset. The test dataset, however, presented lower accuracy.

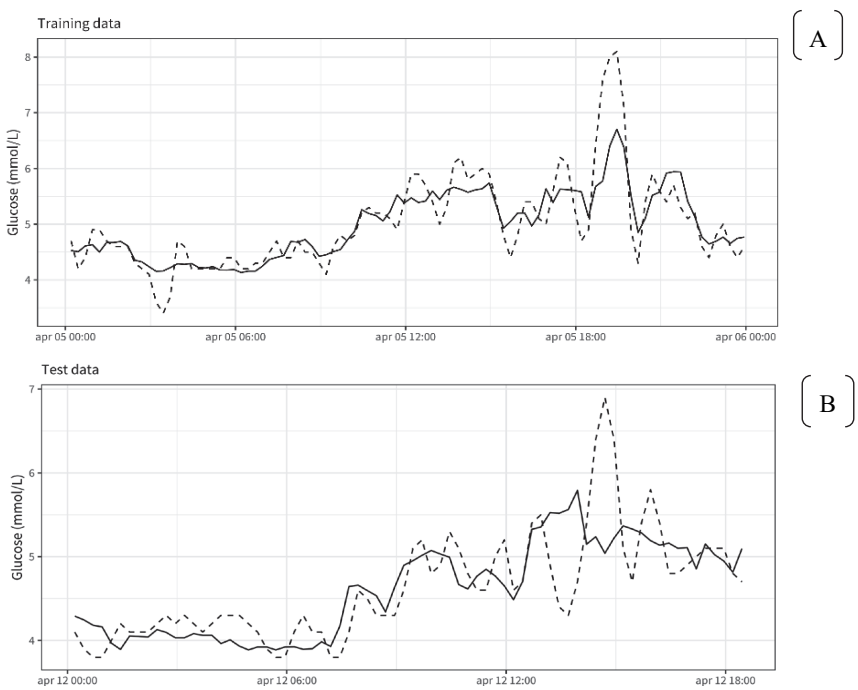

Figure 4. *Goodness-of-fit model performance on example training data (A) and test data (B). Data come from subject 09.*

3.3. Predicting Lifestyle Behavior Effects Based on Interstitial Glucose Levels

The glycemic response is highly personal, depending on biological and contextual factors, such as lipid metabolism, muscle mass, nutrition, stress, activity, and sleep. The individual glycemic response may, thus, vary between and within individuals. Here, we applied an

extreme gradient boosting machine approach with the subject number as a random variable to allow personalized models to predict glucose levels from contextual factors in real time. Continuous glucose levels for three days were predicted from 72 features engineered around nutrition, activity, and sleep over different periods (short term: 3 h, long term: 8 h, and 24 h). An overall mean absolute error (MAE) of 0.32 (+/− 0.04) mmol/L for the training data and 0.62 (+/− 0.15) mmol/L for the test data was obtained. Figure 4 shows an example of the goodness of fit for subject 09 from the training dataset (Figure 4A) and the test dataset (Figure 4B). Bland–Altman analysis indicated a bias lower than 0.01 mmol/L in both the training and the test set and 2.5 and 97.5 percentile limits of agreement ranging from −0.72 to 1.1 in the training set and from −1.56 to 1.8 mmol/L in the test set (Figure 5).

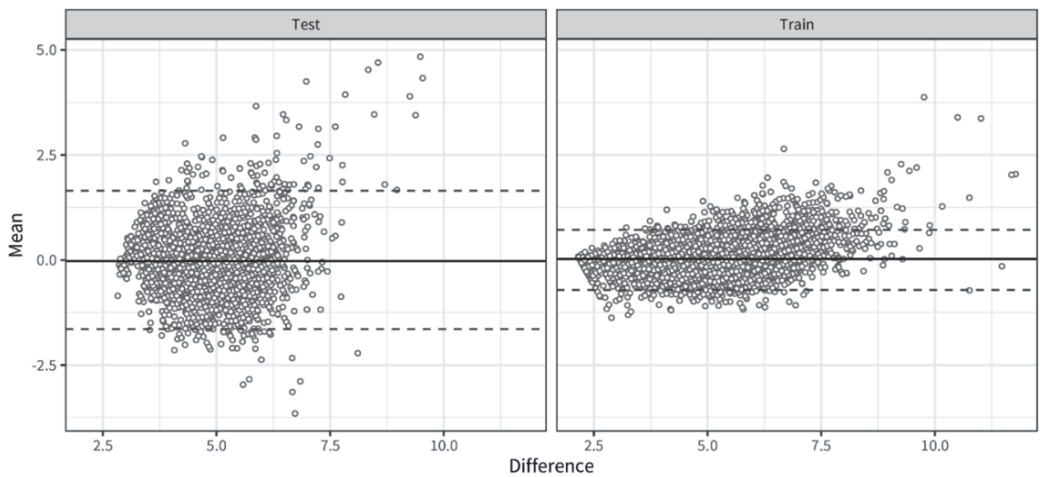

Figure 5. *Bland–Altman analysis indicated a bias lower than 0.01 mmol/L in both the training and the test set and 2.5 and 97.5 percentile limits of agreement ranging from -0.72 to 1.1 in the training set and from -1.56 to 1.8 mmol/L in the test set.*

The final model contained 17 features after feature selection, covering activity, nutrition, sleep, and unexplained, subject-specific features. The influence of the different features is summarized in Table 1, and the details are specified in Supplementary Table 1. The influence of cardiometabolic factors was 26.7%, while the contribution of the unexplained, subject-specific features was 24.1%. The influence of short- and long-term activity was 10.9% and 12.5%, respectively. The short- and long-term nutrition features had an influence of 10.7% and 8.7%. Finally, the contribution of the sleep features was 10.7%. Although these numbers indicate an overall insight into the importance of the features in predicting glucose levels, they may have been very different between and within individuals across the study period. To provide personalized insights into the relationship between the contextual factors and glucose levels, we applied the SHAP (Shapley additive explanations) procedure to the selected model. With the goal of personalized insight being to reduce high glucose peaks, high glucose peaks were identified for each participant. Shapley values were then calculated for each of those glucose peaks to determine the feature influence for those specific glucose

data points. Figure 6 shows the frequency of the five most important features per data point per participant when explaining their highest peaks. Overall, there was no specific category of features that was important for explaining the highest peaks, but, at the individual level, some features occurred more frequently. For example, sleep duration was never important when explaining the glucose peaks of subjects 15 and 19, while, for subjects 9 and 10, it was a relatively frequent feature. As another example, the glucose peaks of subject 22 were most often explained by their energy expenditure over the last 24 h and their subject-specific model intercept. This may indicate that the glucose peaks for this participant were related to the subject-specific variance that remains unexplained by the features thus far included in this model.

Table 1. *Overall feature influence of the different contextual modalities, activity (accelerometry), nutrition (carbohydrates, calories), and sleep (sleep duration, deep sleep duration), as well as cardiometabolic factors (energy expenditure, average heart rate) and a subject-specific factor.*

Group	Weight
Cardiometabolic factors	26.7%
Subject	24.1%
Activity—Long term	12.5%
Nutrition—Short term	10.9%
Sleep	10.7%
Nutrition—Long term	8.7%
Activity—Short term	6.5%

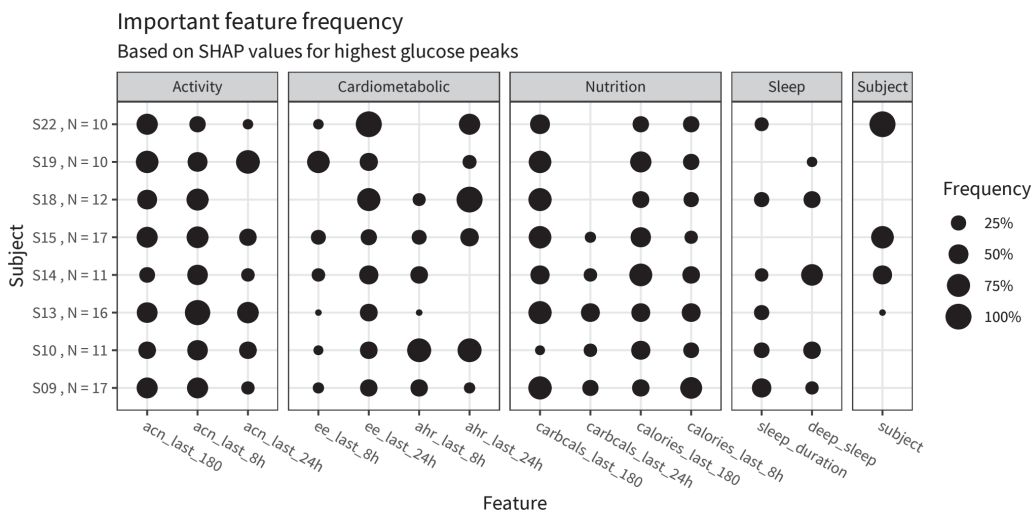

Figure 6. *Frequency of use of the five most important features in the prediction of selected glucose peaks for individuals where more than 10 such peaks could be identified. The y-axis denotes the subjects and the number of peaks identified in each subject. ee: energy expenditure, acn: acceleration, ahr: average heart rate.*

4. DISCUSSION

In this study, we aimed to prove the feasibility of using real-life CGM data combined with contextual data to make predictions on an individual basis in healthy persons. First, we showed the ability to predict eating moments using interstitial glucose. Second, we showed the ability to predict and explain current interstitial glucose values using contextual data, including those relating to food intake, physical activity, and sleep.

4.1. Meal Detection

Dietary intake assessment is challenging since common methods are susceptible to misreporting. Several technological innovations currently focus on image recognition of meal photographs, eating action detection, and biochemical sensors that are targeted at specific nutrition-associated metabolite concentrations in non-invasive biofluids such as urine and sweat [37]. These innovations cover different aspects of dietary intake assessment, ranging from quantifying meal composition and intake of specific nutrients to meal timing. Here, we used continuous glucose monitoring with a gradient boosting machine algorithm to predict eating actions. The resulting model showed excellent performance on the training set, with an accuracy, specificity, and sensitivity of more than 90%. For the test set, the performance was moderate to good, with an accuracy of 76%, specificity of 60%, and sensitivity of 78%. The reason that the test dataset presented with a lower accuracy was possibly related to variable behavior or inconsistent food logging within the individuals—indicated by highly variable kcals/day recorded by individuals—making the model not fully generalizable across the full study period. Future work could include a reinforcement learning approach to continuously update the algorithm specifically for an individual. Otherwise, a more controlled approach against a ground truth reference, for example, with video camera monitoring of eating moments, may be applied to further investigate this and improve the algorithm upfront. To our knowledge, this is the first study demonstrating a prediction algorithm for eating moments in a healthy population in a real-life setting. Most studies on meal detection using CGM data so far have focused on T1D, with the potential for automated timing of insulin administration, for instance, in an artificial pancreas [35,36,38]. Sensitivity rates in some of these studies, if reported, were higher compared to the sensitivity of our model, but, as the glucose response to meals in people with T1D is faster and higher as there is no compensatory action from insulin, these results cannot directly be compared. The potential application of meal detection in a healthy or a (pre-)T2D population is different and may, therefore, require different levels of accuracy, sensitivity, and specificity than those required in the case of medical purposes. In T1D patients, meal detection is applied to control insulin administration, whereas, in a healthy or a (pre-)T2D population, meal detection can be used to provide individuals with more insight into their eating behavior and may provide opportunities for personalized feedback on frequency or timing of eating moments. In the future, it may even be possible to predict both meal timing and dietary composition from CGM data [39], which would provide even more opportunities for personalized advice to

stimulate behavior change. Meal detection algorithms could also play a role in improving the quality of food diary applications. The collection of food intake data is known to be subject to misreporting [34]. Active recall using notifications via a smartphone app after the detection of a meal moment, could, for example, aid in improving compliance with food intake data collection.

4.2. Predicting Glucose

Personalized nutrition is gaining momentum in science to support health maintenance and disease prevention, especially prevention of chronic, lifestyle-related diseases such as type 2 diabetes [31,40,41]. While personalized nutrition approaches still require relatively invasive measurements in a standardized clinical setting, here, we set out an approach that allows personalized nutrition monitoring in everyday life using CGM, activity tracking, sleep monitoring, and a food diary. For predicting glucose levels using contextual data, we engineered 72 features from physical activity, meal composition, and sleep data, which were used to train an extreme gradient boosting algorithm. We engineered both short- and long-term features for physical activity and nutrition, as research has shown that both physical activity and nutrition have an acute as well as a more long-term effect on glucose levels [42–46]. The recursive feature elimination (RFE) step provided a subset of features by eliminating features with redundant information. This subset provided similar final model performance as when all features were included. This reduction in the number of features aided the interpretation of the final model and decreased training times. The feature selection method influenced which feature became part of the final model, and, as such, the final model did not cover all possible relationships of the full set of features with the glucose response. The choice of the feature selection algorithm, therefore, was an important consideration regarding the result.

The overview of the final, overall feature influence confirmed the importance of physical activity, dietary intake, and sleep in determining glucose values [47–50]. In the overall model, physical activity and nutrition had a comparable influence on interstitial glucose values (Table 1). Research in T2D has, indeed, shown that structural, physical activity of more than 150 min per week is associated with a greater decline in HbA1c than lower amounts of physical activity [51]. Alternatively, the long-term physical activity features in our model may also serve as a proxy for prolonged sedentary behavior, which has also been associated with higher glucose values [52,53]. Future development of activity tracking should explicitly separate physical activity from sedentary behavior to improve personalized insight into their relation to glucose concentrations. Interestingly, two other studies showed a larger contribution of meal composition than that of physical activity, while comparable features for nutrition were used (number of calories, protein, sugar, fat, and carbohydrates over a specific time window) [31,54]. While the importance of physical activity in our model and that of Bent et al. was comparable (17% and 19%, respectively), the influence of nutrition was lower in our model (20% and 37%, respectively) [54]. Possibly, this is explained by the

fact that they focused on persons with prediabetes only, while the current study targeted a healthy population. Although it should be noted that prediabetes was not excluded, 16 out of 24 participants had a fasting plasma glucose below 5.6 mmol/L. As persons with prediabetes are already insulin resistant, a higher postprandial glucose response after consumption of carbohydrate-rich foods compared to that of a healthy population is to be expected. Berry et al. also indicated greater influence of nutrition, while including healthy people [31]. However, in their study, only the effects of standardized meals over a short time frame were investigated, and subjects were instructed to limit exercise on test days. This may explain why meal composition as compared to physical activity was more important in their model. Finally, sleep, as a lifestyle-related factor, had a significant influence on interstitial glucose concentrations, albeit less than nutrition and physical activity (11%). This is in concordance with the aforementioned personalized nutrition studies investigating the influence of contextual factors on glucose control [31,32]. Indeed, sleep disturbance is linked to impaired glucose control, while sleep interventions may contribute to its normalization [55]. In addition to contextual lifestyle factors, cardiometabolic features (energy expenditure, average heart rate) and an unexplained, subject-specific feature were identified as influencing glucose levels. This confirms previous findings showing that there is a large interindividual variability in glucose response, which can only partly be explained by measured contextual factors [32,40,56]. Adding other factors such as psychological stress, genetics, metabolic health, cardiovascular health, anthropometry, and demography may further increase the predictive power of the model [57–59]. However, as the relative contribution of the unexplained, between-person variation was less than 25%, one may want to be mindful of adding burdensome or expensive measurements such as genetics and blood biomarkers considering their probable limited impact on the model.

The strength of this study is the real-world design, maximizing the ecological validity of the observations. However, neither above-described applications of remote monitoring technologies can be realized without proper data quality. Therefore, only participants with a professional affinity for nutrition research and care were included. Indeed, the data from food logs appeared very complete, although this was not directly verifiable with reference data. Still, from the 24 participants, only 11 individuals had good-quality multimodal data for three consecutive days from the HowAmI app, the wristband, and the continuous glucose monitor (Figure 2. For the seven excluded participants, this was explained by specific problems regarding the ease of use of the research-grade wristband and the accompanying software, causing episodes of the device not collecting activity and sleep data in parallel to collecting glucose data. In particular, the software was primarily intended for researchers not for study participants and, therefore, not very user-friendly. Training and a 24/7 helpdesk were provided to anticipate the issues, but, unfortunately, this was not sufficient to obtain 100% data quality. Ideally, for a real-world design, data transfer is wireless without the need for active contributions from the participants. While there are devices available allowing such passive data collection and transfer, we still chose to use this device given its ability to collect

raw data. Six participants were excluded because of incomplete continuous glucose monitoring data. While participants were blinded to the glucose data to make sure it did not influence their behavior, confounding the study results, they were also not able to observe whether actual data were collected. Hence, it was only after the study that these missing data were identified. On-device alarms on erroneous data collection could help participants to act earlier by replacing devices and improving continuous glucose data collection. Overall, these insights confirm the fact that results and outcomes from remote clinical trials strongly depend on data quality, correct use, and the connectivity of sensor technologies [25]. This stresses the need for easy-to-use digital devices in remote clinical trials [60,61]. Further remote investigations should expand on the current study, increasing sample size with a particular focus on easy-to-use digital devices. Another strength of the current research was the use of techniques to maximize personalized insights into contextual glucose relationships. A practical problem with machine learning models being used to capture the complex, non-linear relationships is their interpretation. The Shapley additive explanation (SHAP) approach was applied to explain the feature influence on the highest glucose levels for an individual. This approach is extensively utilized for explaining 'black box' machine learning models, allowing the calculation of the model features' contribution to each individual data point [62]. Here, we selected the top 10 highest glucose levels to calculate the most important features contributing to those peaks for each participant. While, overall, activity-related features have a large influence on glucose levels, at an individual level, sleep or nutrition may be more important. Shapley values could, thus, form the basis for actionable insight into personalized lifestyle recommendations.

5. CONCLUSIONS

In this study, we explored the feasibility of data generated from current, wearable technologies for detecting eating moments and predicting the impact of physical activity, sleep, and dietary intake on continuous glucose levels in healthy volunteers. We showed that, pending further validation in a larger population, both eating moments and the influence of contextual lifestyle factors on glucose can potentially be predicted on an individual level. By opening the 'black box' using SHAP, to our knowledge, this is the first study taking the step towards personalized, real-time lifestyle recommendations based on continuous health monitoring data. Eventually, the application of digital biomarkers that predict glucose from contextual factors is to drive personalized, continuous feedback on lifestyle factors to improve or maintain glucose homeostasis, thereby preventing the development of T2D.

The ease of use of wearable technologies is key for good data quality to allow for application in remote clinical trials, self-management, or remote care. Under everyday life conditions, we showed the feasibility of detecting eating moments to support food intake monitoring. Additionally, we showed how machine learning methods can be used to understand and explain individual relations between contextual lifestyle factors and interstitial glucose

concentrations. Pending further validation, it is envisioned that these technologies will support self-management to maintain a healthy glucose metabolism through personalized lifestyle recommendations. Especially when combined with the early detection of insulin resistance and understanding of the biological cause for glucose derailment, the possibility exists that, in the future, meaningful digital biomarkers may provide the feedback and motivation to enable individuals to achieve the required lifestyle behavior change, ultimately allowing them to maintain health, prevent disease development, and reduce the economic burden of chronic diseases such as T2D.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Supplementary Table S1. Feature importance of the different contextual modalities, activity, nutrition, and sleep, as well as the between-individual variation.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets presented in this article are available upon reasonable request. Requests to access the datasets should be directed to willem.vandenbrink@tno.nl.

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7

DIFFERENTIAL EFFECTS OF LIFESTYLE INTERVENTIONS ON CONTINUOUS GLUCOSE MONITORING METRICS IN PERSONS WITH TYPE 2 DIABETES: POTENTIAL FOR PERSONALIZED TREATMENT

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Submitted

ABSTRACT

Objective: The effects of lifestyle on glucose metabolism significantly differ between individuals. Hyperglycemia in type 2 diabetes is driven by tissue-specific insulin resistance and reduced beta-cell capacity, whose relative contribution varies between persons, potentially affecting the impact of lifestyle interventions. We quantified effects of lifestyle on continuously measured glucose (CGM) metrics and evaluated how these differ between type 2 diabetes phenotypes.

Research Design and Methods: Forty persons with type 2 diabetes wore a CGM for 11 periods of 4 days, of which 3 control and 4 duplicated intervention periods (2x low carbohydrate diet, 2x Mediterranean diet, 2x walking after each meal and 2x 'active day' (hourly 5-minute exercise bouts)). Tissue-specific insulin resistance and beta-cell function were quantified using an OGTT. A linear mixed effects model quantified lifestyle impact on CGM metrics.

Results: On overage, low carbohydrate diet, walking after meal and active day, but not the Mediterranean diet, resulted in lower mean glucose (7.74, 8.37, 8.40 and 8.70 mmol/L, respectively) as compared to control (8.66 mmol/L) in participants who did not restrict carbohydrate intake at baseline. Notably, the magnitude and direction of effects varied between individuals. For instance, the low carbohydrate diet had more beneficial effects for persons who had liver- or combined insulin resistance with poor beta-cell function than for individuals who only had poor beta-cell function.

Conclusions: On average, traditional lifestyle interventions improved CGM metrics within 4 days. Importantly, the effects appear to vary depending on the diabetes phenotype, thus pointing to the need for personalized lifestyle treatment.

1. INTRODUCTION

Type 2 Diabetes is a chronic metabolic disorder characterized by insulin resistance and dysglycemia. Lifestyle modifications, including adopting a healthy diet, increasing physical activity and losing weight, can improve glycemic control and insulin sensitivity, thereby mitigating diabetes-related complications [1–3]. The Look AHEAD trial has demonstrated that adopting a healthier lifestyle can delay progression of type 2 diabetes [4]. However, the impact of lifestyle interventions varies greatly between individuals, with high interindividual variability in the postprandial glucose response to identical foods [5,6], and differential responses to dietary interventions between normoglycemic and (pre-)diabetic people [7]. In view of the inherent heterogeneity of the disease [8], it seems quite conceivable that the efficacy of lifestyle interventions is not uniform across individuals with type 2 diabetes, and that personalization of dietary advice or physical activity regime may be required for optimal glycemic control [9].

Most lifestyle intervention studies so far were medium to long-term, group-based, and focus predominantly on HbA1c as measure of glycemic control. HbA1c, however, does not reflect acute glycemic excursions and events such as hypoglycemia or postprandial hyperglycemia [10]. Since the introduction of continuous glucose monitoring (CGM), it has been established that CGM-derived measures of glycemic control are clinically relevant [10,11] and linked to all-cause mortality and risk of macro- and microvascular complications [12,13]. A CGM system provides real-time (interstitial) glucose concentrations and can be used to calculate widely accepted metrics that reflect not only mean glucose, but also measures of glycemic variability as well as time in, below and above target ranges [10,11]. CGM can thus provide insight in short term effects of lifestyle on glycemic control.

Short term glycemic variations may differ between diabetic phenotypes, as the severity of insulin resistance may differ between various insulin-sensitive tissues [14]. It has been suggested that the diabetic phenotype or “diabetype”, based on the predominant location of insulin resistance (i.e., muscle, liver, or both) and the remaining capacity of beta-cells to produce insulin, may affect the response to different dietary interventions [15–17]. Also, physical exercise may be especially effective in improving glycemic control in people who are predominantly affected by muscle insulin resistance [18]. Insight in the differential effects of lifestyle interventions on glucose management among individuals with distinct diabetypes may contribute to more personalized lifestyle recommendations. Here, we aimed to explore the (sub)acute effects of distinct lifestyle interventions on CGM metrics in people with T2D, and the impact of their “diabetype” in this context.

2. RESEARCH DESIGN AND METHODS

2.1. Study Population

41 men and women with type 2 diabetes, as diagnosed by a physician, using either lifestyle and/or metformin for managing glycemic control were recruited via general practitioners (GPs), social media and newspaper advertisements. Participants were eligible if they met the following inclusion criteria: Body Mass Index (BMI) 25 – 40 kg/m2, preferably < 35 kg/m2, insulin-naive, able and willing to provide informed consent, and willing to comply with all study procedures. The main exclusion criteria were history of or planned (bariatric) surgery or MRI in the next six months, chronic medical conditions, medication use interfering with glucose metabolism, and Coeliac or Crohn's disease. A complete list of exclusion criteria can be found on https://www.onderzoekmetmensen.nl/en/trial/24321. Baseline characteristics are shown in **Table 1.**

Table 2. *Baseline characteristics of 41 participants with type 2 Diabetes Mellitus*

	n	**Mean**	**SD**
Sex (male/female)	22 / 19		
Education (lower / higher)	15 / 26		
Treatment (yes / no metformin)	25 / 16		
Age (y)		62.3	7.2
Diabetes duration (y)		9.7	6.5
BMI (kg/m2)		29.2	3.8
HbA1c (% (mmol/mol))		7.1 (54.5)	3.5 (14.8)
Insulin fasting (mU/L)		12.05	8.90
C-peptide fasting (nmol/L)		0.87	0.42
Hepatic Insulin Resistance Index (HIRI)		1812	1362
Muscle Insulin Sensitivity Index (MISI)		-3.60	4.23
Disposition Index (DI)		0.72	0.53
Total cholesterol (mmol/L)		4.67	1.13
LDL-cholesterol (mmol/L)		2.91	1.00
Triglycerides (mmol/L)		1.46	0.72
C-Reactive Protein (CRP) (mg/L)		2.27	2.49
Systolic blood pressure (mmHg)		160.4	17.9
Diastolic blood pressure (mmHg)		91.2	14.4

2.2. Study procedures

At the start of the study, a clinical visit was planned during which anthropometry (height (first visit only), bodyweight, waist- and hip circumference) and blood pressure were measured according to standard operating procedures, and online questionnaires were completed.

Hereafter, participants followed 11 four-day monitoring periods in a randomized crossover design (**Figure 1**). During three control periods, glucose was monitored in daily life, while the impact of two dietary- (low carbohydrate diet and Mediterranean diet) and two exercise-based interventions (walk after meal and active day) on CGM metrics was measured during eight intervention periods. During all periods, participants were instructed to use a continuous glucose monitor (CGM) monitor physical activity and sleep, and register food intake, medication use and wellbeing via a custom smartphone application. Participants were asked to calibrate their CGM system every morning using a finger-prick and manual blood glucose measurement device (Accu-Chek Instant, Roche, Basel, Switzerland).

Figure 1. *study design*

At the end of or just before each control period (week 2, 13 and 24), participants came to the clinic for an Oral Glucose Tolerance Test (OGTT). After the first control period (week 2), each participant underwent four lifestyle interventions in a randomized order. The second control period was planned after the first series of intervention periods (week 13), after which all four interventions were repeated in a randomized order. Subsequently, the last control period and OGTT were performed (week 24). All control and intervention periods were separated by at least one week wash-out period. The study ended with a clinical visit during which anthropometric and blood pressure measurements were repeated (week 27). Helpdesk support was available throughout the study. The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19). The study was performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Dutch Trial Register: NL7848. All participants provided written informed consent.

2.3. Interventions

During the "Active day" (AD) intervention, participants were asked to perform moderate to intense physical exercise (e.g., brisk walking, climbing the stairs or knee bends) for 5 minutes every hour between 09:00 and 17:00 hour to reduce sedentary time. During the "Walk after

meal" (WaM) intervention, participants were asked to walk for 15 minutes after each breakfast, lunch, and dinner to reduce postprandial glucose levels. During the "Low carbohydrate diet" (LC) intervention, participants were instructed not to exceed a maximum intake of 100 grams of carbohydrates a day. During the "Mediterranean diet" (Med) intervention, participants were instructed to eat a diet high in fruits, vegetables, nuts, fish, whole grain, and olive oil. During both dietary interventions, for breakfast, lunch and snacks participants received fitting recipes, and for dinner participants received meal boxes with unprocessed food and recipes for cooking at home from Ekomenu (Amsterdam, the Netherlands).

2.4. Measurements

2.4.1. Self-monitoring devices

The Dexcom G6 Continuous Glucose Monitoring (CGM) System (Dexcom Inc, San Diego, USA) was worn during all monitoring periods and measured the interstitial glucose concentration every 5 minutes. Values were transformed into estimated blood glucose levels by a proprietary algorithm and wirelessly send to participants' smartphone via attached transmitter. Participants applied the Dexcom G6 sensor on the upper arm one day before the start of each monitoring period, to allow for stabilization of the sensor.

Participants used the HowAmI app (TNO, Leiden, The Netherlands) [19], for collecting food intake data. The HowAmI app used the FatSecret food database (Secret Industries Pty Ltd., Victoria, Australia) to access detailed food and nutrition data and connected to a custom, parallel back-end database to record food intake and the time stamp for each meal.

The Fitbit Charge 3 activity tracker (Fitbit, San Francisco, CA, USA) was used to measure daily physical activity in Metabolic Equivalent of Tasks (METs) and sleep in hours. Data was collected and stored using Fitabase (Small Steps Labs, San Diego, CA, USA) prior to analysis.

2.4.2. Oral glucose tolerance test and diabetyping

An OGTT was performed to assess plasma glucose and insulin response to a standardized glucose solution (75 g of glucose dissolved in water) for subsequent calculation of indices of the level of insulin resistance (IR) in different organs and beta-cell function (BCF). To measure plasma glucose and insulin levels, venous blood samples were taken before as well as 30, 60, 90 and 120 minutes after consumption of the sugar water. Blood glucose and insulin concentrations were used to calculate the following three indices used for "diabetyping": (1) the hepatic insulin resistance index (HIRI); (2) the muscle insulin sensitivity index (MISI); and (3) the disposition index (DI) as a measure of pancreatic beta-cell function [14,20–22]. A combination of liver and/or muscle IR with or without impaired BCF resulted in a total of eight possible subgroups ("diabetypes") [23].

2.4.3. Questionnaires

Questionnaires were completed via an online portal, and included questions on demographics, lifestyle, diabetes duration and treatment. Regular dietary intake before study participation was assessed using the online 183-item Food Frequency Questionnaire (FFQ) developed by Wageningen University and Research [24,25]. Sleep was assessed using the Pittsburgh Sleep Quality Index, a questionnaire which assesses self-rated sleep quality and disturbances in the past month [26,27].

2.5. Statistical Analysis

Statistical analyses were performed using R software [28]. To check compliance with the lifestyle interventions, compliance scores for the LC, AD and WaM intervention were calculated. For the Med intervention no compliance score was calculated as adherence to the Mediterranean diet is not easily quantifiable. For the LC intervention compliance was defined as days during which carbohydrates (CHO) contributed < 26% to total caloric intake [29,30]. For the WaM intervention compliance was defined as days with ≥ 4 periods of physical activity for ≥ 10 minutes. For the AD intervention compliance was defined as days with ≤ 4 sedentary periods of ≥ 2 hours of inactivity; four consecutive sedentary periods of two hours or more were interpreted as sleep.

CGM metrics were calculated per person, per 4-day measurement period. Mean glucose, coefficient of variation (CV), time in range (TIR; > 3.9 & < 10.0 mmol/L), time above range level 1 (TAR-L1; >= 10.0 & < 13.9 mmol/L), time above range level 2 (TAR-L2; >= 13.9 mmol/L), time below range level 1 (TBR-L1; > 3.0 & <= 3.9 mmol/L), time below range level 2 (TBR-L2; <= 3.0 mmol/L), and mean amplitude of glucose excursions (MAGE) were calculated according to an international consensus statement [31].

A random effects multilevel model was used to quantify the effects of the four lifestyle interventions on CGM metrics with participant as random effect (null models). Time was tested as a covariate, but this showed no effect on CGM metrics nor model improvement. This indicates that our assumption that 4-day interventions followed by at least a week of wash-out indeed avoided longer term effects of and carry-over effects between interventions. Subsequently, a binary variable reflecting CHO consumption prior to the study, as assessed by FFQ, was added to the null model. Specifically, the study population was split into two groups, a “normal carb” group consuming more than 26% of calories as CHO at baseline, and a “low carb” group eating less than 26% of calories as CHO [29,30]. Adding this variable improved the performance of all models for CGM metrics (intermediate models). Lastly, the impact of further adding diabetype and interaction-effects on model performance was assessed (final models). Only diabetypes assigned to at least 10 participants at any point in time during the study were included in the models to allow for sufficient power in the models. As for some individuals the diabetype changed during the study (supposedly affected by lifestyle interventions), the diabetype defined by the most recent OGTT was used for the next

monitoring period in the model. Diabetypes assigned to at least 10 participants were 1) isolated impaired BCF (PB; n=16); 2) hepatic IR and impaired BCF (PB-HIR; n=30); and 3) both hepatic and muscle IR and impaired BCF (PB-HMIR; n=11), where 17 persons had two distinct phenotypes over time. Model performance for all CGM metrics but TAR-L2 improved significantly when the three most common diabetypes, PB, PB-HIR and PB-HMIR were added (Supplementary Table 1). Therefore, separate models were made for each diabetype assigned to at least 10 participants during the entire study to assess which lifestyle interventions sorted the most beneficial effects for each of the three diabetypes. The amount of CHO consumed at baseline (as measured using the FFQ) interacted with intervention effects on CGM metrics and was therefore also included in the models for the PB-group and PB-HIR group. In the PB-HMIR group there was only one participant with a low CHO intake at baseline, who was therefore excluded from the analysis. The final models included intercept, intervention, and for two subgroups (PB and PB-HIR) also CHO consumption at baseline as well as its interaction with intervention as fixed factors, and participant as random effect.

2.6. Data and Resource Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the data being generated as part of a public private partnership and shared intellectual property with partners but are available from the corresponding author upon reasonable request.

3. RESULTS

3.1. Compliance with lifestyle instructions

Subjects were 100% compliant with AD instructions, while compliance with WaM and LC instructions was 79% on average.

3.2. Control periods

For the total study population, glucose levels were in range for an average of 82.4% of time and above range for 17.4% of time during the control conditions. Time below range was less than 1% for all study periods and was therefore excluded from analyses. Nine participants were accustomed to consuming less than 26% of calories as CHO on average (as measured by FFQ) to control glycemia even before study participation. In control conditions, their CGM metrics were clearly different from those of participants who consumed more CHO (n=29) (Figure 2). According to the model, TIR was 12% higher, although non-significant, and CV and MAGE were significantly lower (-3.86% and -1.47 mmol/L respectively) in participants consuming <26% of calories as CHO (supplementary Table 2).

3.3. Effects of lifestyle interventions on average CGM metrics

Quite conceivably, the effects of interventions on CGM metrics were different in persons who deliberately restricted carbohydrate intake at baseline from those in participants who did not (figure 2, Supplementary Table 2). Indeed, LC clearly reduced Mean, TAR-L1/L2 and MAGE in participants consuming more than 26% of calories as CHO at baseline. However, in participants consuming less than 26% of calories as CHO at baseline, this effect was significantly lower for Mean, TIR, TAR-L1 and MAGE. In contrast, AD and WaM similarly benefitted several CGM metrics in both groups, while Med deteriorated various metrics, particularly in participants restricting CHO at baseline (although it also induced a slight increase of TAR-L2 and CV in those who did not).

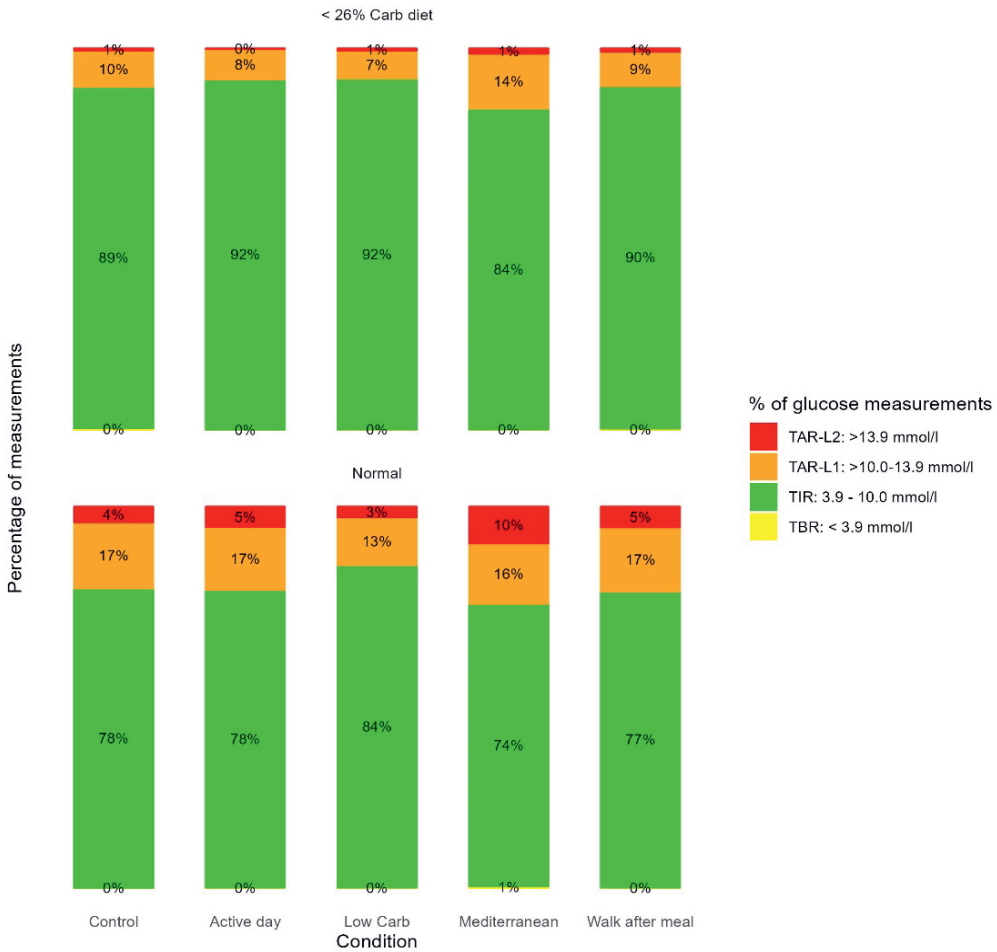

Figure 2*. TIR, TBR and TAR expressed as an average percentage of total time spent in this range for participants consuming >26% of calories from carbohydrates at baseline (upper bars) and for participants consuming <26% of calories from carbohydrates at baseline (lower bars).*

3.4. Interindividual differences in effects of lifestyle interventions on CGM metrics

Inspection of individual glucose profiles revealed apparent differences between individuals in terms of response to lifestyle intervention (Figure 3). For example, in subject 10, the mean glucose appears to improve in response to the LC, WaM and AD interventions, while TAR seems to decline during LC and AD interventions. Glucose variability seems to be lowest during LC intervention. In contrast, in subject 14, mean glucose, TIR and glucose variability seem to improve in response to all but the AD intervention. In subject 71, CGM metrics appear to remain unaffected by any of the interventions.

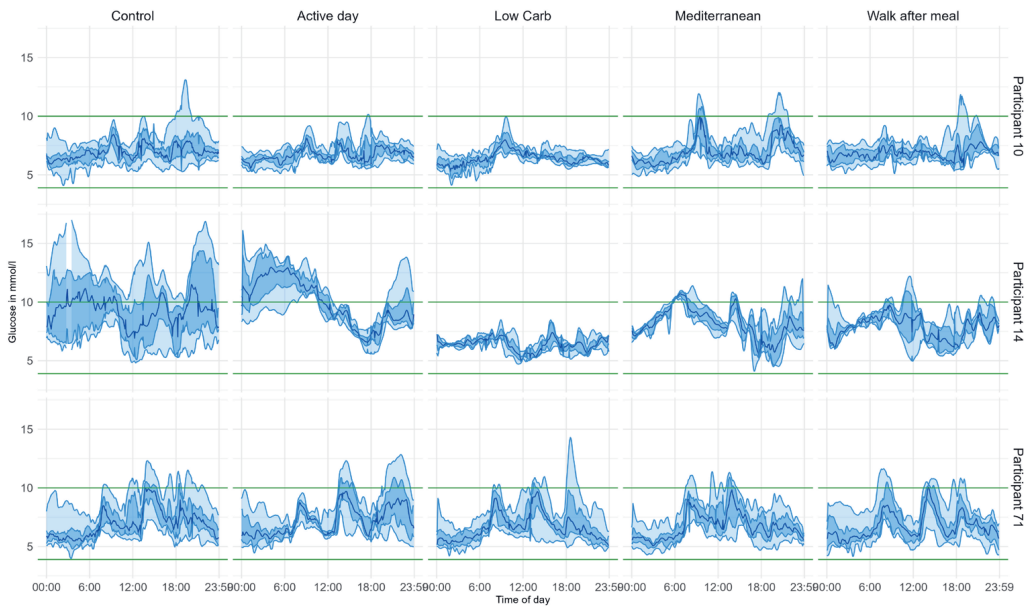

Figure 3. *Ambulatory glucose profiles during the control periods and the four intervention phases for three participants. The target glucose range (3.9-10.0 mmol/l) is shown as two parallel lines. The dark line is the median line, which is based on a rolling mean glucose, and shows whether the average glucose is within the target glucose range and how much it oscillates during the day. The darker shaded band represents the 25th–75th percentile and shows the 50% of all glucose values that are closest to the median line and their variability from day to day. The lighter shaded band represents 90% of all glucose values that are closes to the median line.*

3.5. Impact of diabetes phenotype on effects of lifestyle intervention

Further analysis was done to examine if interindividual differences could be explained by differences in diabetes phenotype or ‘diabetype’. Figure 4 shows the differences in TIR and TAR-L1/2 between the control and intervention periods per diabetype. During control periods, the PB-HMIR group had a lower TIR and higher TAR-L1/L2 than the PB group and PB-HIR group. Coefficients of the final models including either one of these diabetypes are listed in Supplementary Table 3. The data provides clues as to which lifestyle intervention improved CGM metrics most in each diabetype.

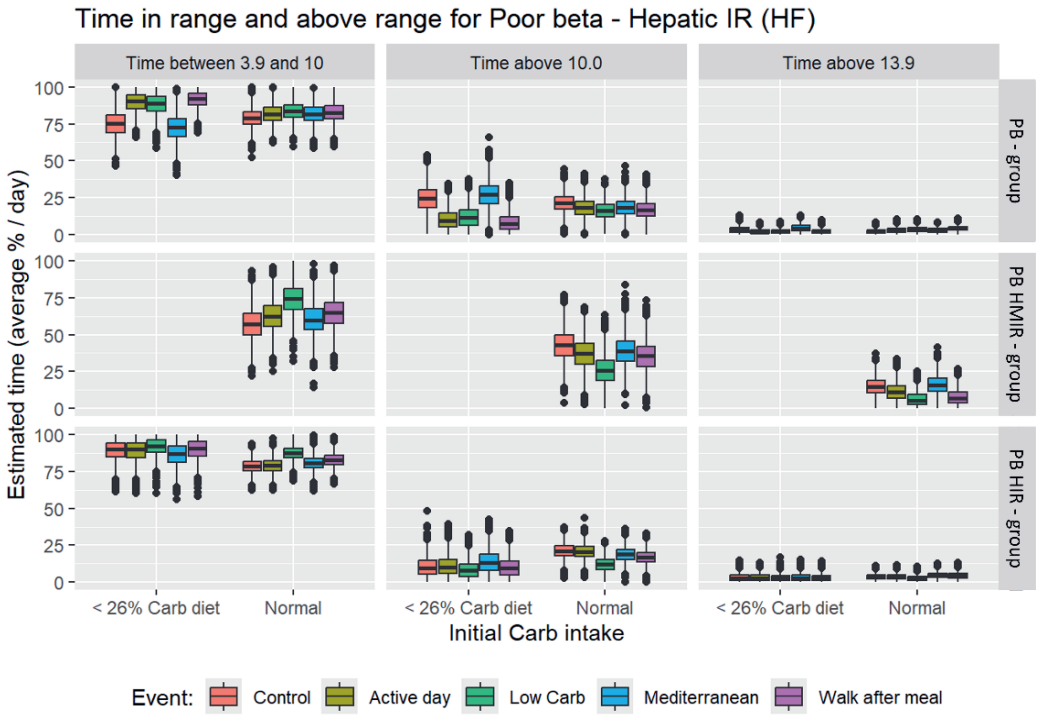

Figure 4. *Boxplots showing TIR and TAR level 1 and 2 in average percentage per day for control and intervention periods, per diabetype: PB, PB-HIR, PB-HMIR. In figure A and B results are presented separately for participants consuming > 26% of calories as carbohydrates, and participants consuming < 26% of calories as carbohydrate at baseline.*

In people with isolated impaired BCF, AD and WaM increased TIR (and reduced TAR-L1 and TAR-L2) only in those who restricted CHO intake at baseline (n=5). LC had no significant effects in this group. For participants in the PB-group with normal CHO intake at baseline, LC intervention resulted in a significantly lower mean glucose and MAGE. The Med intervention resulted in a higher CV and MAGE in those who restricted CHO at baseline and had no impact on participants with normal CHO intake at baseline.

In people with impaired BCF and hepatic IR (PB-HIR), LC, and to a lesser extent WaM, increased TIR and reduced TAR-L1 (and TAR-L2 for LC), especially in those with normal CHO intake at baseline. Additionally, LC decreased mean, CV and MAGE. For those who restricted CHO intake at baseline (n=6) beneficial effects of LC on mean and MAGE were significantly lower as compared to those with normal CHO intake at baseline. Med resulted in a significant increase in mean, MAGE and TAR-L1 and decrease in TIR only in those who restricted CHO intake at baseline and increase in TIR-L2 for those with normal CHO intake.

In people with impaired BCF and combined IR (PB-HMIR), largest improvements were seen with LC and WaM, which significantly improved all CGM metrics, but CV. AD resulted in a

small but significant decrease in mean and MAGE, and an insignificant increase in TIR and decrease in TAR L1/L2.

4. DISCUSSION

Within 4 days, various lifestyle interventions improved CGM metrics in patients with type 2 diabetes. The low carbohydrate intervention (LC) had the most pronounced effects, followed by the walk after meal (WaM) and active day (AD; hourly 5-minute exercise bouts) interventions. The Mediterranean diet (Med) did result in a small negative effect on TAR-L2 and CV. In the group with isolated poor BCF, LC intervention only had a modest effect on mean and MAGE. WaM and AD decreased TAR-L1 and increased TIR, but only in those with restricted CHO intake at baseline. In people with hepatic IR and poor BCF, especially LC and to some extent WaM had favorable effects on CGM metrics. The Mediterranean diet had a minor negative effect only in this group, which was more pronounced in the subgroup consuming a low carbohydrate diet at baseline. In people with combined IR and poor BCF, LC and WaM, and to a lesser extent AD, resulted in favorable effects on CGM metrics. These different effects of lifestyle interventions point towards the potential of personalized lifestyle advice based on diabetype and habitual carbohydrate intake.

The low carbohydrate intervention lowered both glucose variability and mean glucose levels in persons with hepatic or combined IR and poor BCF. As expected, the positive effects of the LC intervention were less pronounced in the subgroup already consuming a low carbohydrate diet at baseline. A previous paper reports that a low carbohydrate energy-deficient diet ameliorates liver insulin resistance and blunts basal glucose production more than a high carbohydrate energy-deficient diet in obese subjects without type 2 diabetes [32]. Also, the study by Kirk et al. shows that a short-term intervention including a low carbohydrate diet is more effective in altering hepatic IR as compared to muscle IR. In our study the effects of LC on CGM metrics were largest in the PB-HIR and PB-HMIR groups. The LC intervention was least beneficial in the group with isolated BCF, which is in line with previous research showing that the effectiveness of lifestyle interventions is dependent on the remaining capacity of the pancreas to produce insulin [33].

In a post-hoc analysis of the CORDIOPREV-DIAB study, the Mediterranean diet appeared to improve glycemic control more in type 2 diabetes individuals with muscle- or combined IR than in individuals with isolated liver IR [15]. In our study, the Med intervention had virtually no effects on CGM metrics, except for a (almost across the board) *deterioration* in PB-HIR individuals who restricted their carbohydrate intake at baseline. However, our study investigated the (sub)acute effects of lifestyle interventions on metrics of glucose profiles, whereas the CORDIOPREV-DIAB study evaluated more traditional markers of glucose metabolism, such as HbA1c and the glucose disposition index, over a period of 2 years. Nevertheless, the lack of effect of Med on CGM metrics in our study was unexpected. Indeed, a previous meta-analysis shows that the Mediterranean diet improves glycemic control to a

similar or even larger extent than low-carbohydrate-, low glycemic index- or high protein diets in people with type 2 diabetes [34]. Moreover, in the long term, Mediterranean diets are associated with a reduced risk of CVD in people with type 2 diabetes [35]. We envision several possible explanations for the lack of effect of the Med intervention in our study, including the short duration of the intervention period, the excellent glycemic control at baseline, and the fact that a significant part of the study population took dietary measures to manage their disease even before the study. Indeed, dietary intake during control periods may have been quite like the Mediterranean diet. The Med intervention increased mean glucose, TAR and MAGE, in particular in people with the PB-HIR diabetype who consumed <26% of calories as carbohydrate at baseline, probably because the Med intervention contained more carbohydrate than their usual diet.

A meta-analysis has shown that physical exercise can reduce mean glucose and time above range, but not fasting glucose in people with type 2 diabetes [36]. Accordingly, in our study both the AD and WaM interventions had beneficial effects on mean glucose, TAR-L1, and MAGE. The walking after each meal intervention sorted beneficial effects in people with impaired BCF and combined IR, and to a lesser extent in people with impaired BCF and hepatic IR as compared to control periods. These observations are in line with the expectation that physical activity most effectively improves glycemic control in people with muscle IR [18]. In people with isolated poor BCF, both physical activity interventions resulted in minor negative effects on CGM metrics in persons with a normal carbohydrate intake at baseline, with a higher CV during the AD intervention and a higher TAR-L1 during the WaM intervention as compared to control periods. Interestingly, when only looking at the subgroup already consuming a low carbohydrate diet at baseline, positive effects of the AD and WaM intervention on CGM metrics were observed. So, it seems that a combination of a low carb diet with WaM or AD could help persons with isolated BCF to improve CGM metrics.

Although the interventions in this study were short term, lasting only 4 days, they do provide some indication of long-term effects. Indeed, (sub)acute measures of glycemic control are associated with long-term health outcomes in people with type 2 diabetes. For example, time in range over a couple of days CGM trace is strongly associated with risk of macro- and microvascular complications, such as retinopathy and microalbuminuria [37]. Measures of glucose variability are associated with peripheral neuropathy and all-cause mortality, the latter especially in people with well-controlled glucose status [38]. More acute markers of glycemic control, such as time in range, also allow for personalized treatment plans and tracking of personal goals [39].

It should be noted that baseline glycemia was very well controlled in our study population. Indeed, average time in range was 82% during the control periods, while the American Diabetes Association recommends a time in range (3.9-10 mmol/L or 70-180 mg/dL) of at least 70% [11]. Part of the study population consumed a low carbohydrate diet before the start of the study. These baseline characteristics may well have affected our results, as benefits

of any intervention require room for improvement at baseline. This was also shown by the interaction effects between carbohydrate intake at baseline and some of the interventions. We nevertheless observed significant effects of various interventions, which probably would be even larger in a less well-controlled population. Another limitation is that the continuous glucose monitor was used in unblinded mode. Previous research has shown that the use of a continuous glucose monitor *per se* can drive behavior change in people with type 2 diabetes and thereby contribute to better glycemic control [40]. However, this was not apparent in our study, as there were no changes in CGM metrics over time when comparing the control periods.

In conclusion, lifestyle interventions differentially impacted continuous glucose monitoring metrics in people with type 2 diabetes on short term. The carbohydrate intake at baseline was an important determinant of the impact of any of the lifestyle interventions on CGM metrics. Furthermore, 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 important determinants of the direction and size of the effects of distinct lifestyle interventions. This latter finding suggests that further characterization of the disease phenotype may be of critical importance for optimal lifestyle advice and personalized treatment of type 2 diabetes mellitus.

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DESIGN ISSUES IN PERSONALIZED NUTRITION ADVICE SYSTEMS

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ABSTRACT

The current health status of the general public can substantially benefit from a healthy diet. Using a personalized approach to initiate healthy dietary behavior seems to be a promising strategy, as individuals differ in terms of health status, subsequent dietary needs, and their desired behavior change support. However, providing personalized advice to a wide audience over a long period is very labor-intensive. This bottleneck can possibly be overcome by digitalizing the process of creating and providing personalized advice. An increasing number of personalized advice systems for different purposes is becoming available in the market, ranging from systems providing advice about just a single parameter to very complex systems that include many variables characterizing each individual situation. Scientific background is often lacking in these systems. In designing a personalized nutrition advice system, many design questions need to be answered, ranging from the required input parameters and accurate measurement methods (sense), type of modeling techniques to be used (reason), and modality in which the personalized advice is provided (act). We have addressed these topics in this viewpoint paper, and we have demonstrated the feasibility of setting up an infrastructure for providing personalized dietary advice based on the experience of 2 practical applications in a real-life setting.

INTRODUCTION

Background

Sufficient physical activity and a healthy diet are known to substantially contribute to the prevention of chronic diseases and obesity [1-4]. The increasing burden of chronic diseases, including diabetes, cardiovascular diseases, and obesity, highlights the importance of promoting a healthy lifestyle [5-7]. Dietary and physical activity guidelines have been developed for the general population with the aim to prevent or delay the onset of chronic diseases. However, only a limited number of people adhere to the general guidelines for healthy dietary intake and physical activity [8-12]. In addition, these general guidelines are mostly *one size fits all*, and disregard differences between individuals in terms of biology, behavior, genetics, and the sociopsychological environment [13,14]. Therefore, it has been hypothesized that personalized approaches may be more effective in changing lifestyle parameters such as diet, sleep, stress, and physical activity [15]. Here, we focus on nutrition.

Personalized Nutrition

The overall goal of personalized nutrition approaches is to promote or maintain health status of an individual by using personal data to tailor dietary recommendations or services to fit their specific needs [16]. Personalized nutrition has been defined as approaches that "use individual-specific information, founded in evidence-based science, to promote dietary behavior change that may result in measurable health benefits" [17]. Studies have shown that such personalized approaches are more effective in improving dietary behavior as compared with generic information [18-24]. These personalized nutrition approaches can use the knowledge that individuals may show a differential physiological response to nutrients, foods, or dietary patterns [25,26] but may also be primarily focused on individual (dietary) behavior, preferences, and goals [16,18]. Several factors could explain the high effectiveness of a personalized approach. First, the advice itself is tailored to the individual's constitution and preferences and therefore may be expected to be more effective than generic advice; in other words, if personal data are used for generating evidence-based dietary recommendations, they are more likely to result in health benefits as compared with dietary recommendations based on population data [13,27]. Second, information that is perceived as more relevant by an individual is more likely to receive attention, thereby increasing the impact of the information and the feeling of involvement of an individual [27,28].

Personalized Nutrition Advice Systems

It becomes apparent from the variety of studies performed so far [26,29-32] that personalized advice covers many ways of personalization, ranging from personalization based on a single nutrient (e.g., salt intake and sodium status) to complex systems including a multitude of measurements and associated recommendations. In addition, the mode of delivery for personalized nutrition may vary, including personalized coaching by a dietician, personalized

meal services, and personalized recommender systems such as apps or platforms or combinations thereof [33]. In this paper, we focused on the development and implementation of digital personalized nutrition advice systems (PNASs), in which the translation of individual data into a personalized service is digitalized and (partly) automated. Such PNASs contain 3 common components:

- *Sensing part*, which is made up of the input parameters that are used, such as biomarkers, behavioral data, or genetic information.
- *Reasoning part,* which translates the input parameters into an advice using knowledge rules such as scientifically substantiated food-health relations.
- *Acting part,* where the advice is communicated to the consumer with the aim to help them move toward more healthy habits [16,34].

This is also consistent with Berezowska et al [35], who state that PNASs typically consist of three information process stages forming a feedback loop, describing the relation between a service providing personalized dietary advice (eg, provider of a dietary advice app) and the user of that service: (1) an individual user first provides their personal information, (2) this information is processed to obtain a personalized advice, and (3) it is then communicated to the user of the service. During the development of a digital personalized advice system, a multitude of design choices need to be made on these 3 levels. A schematic overview of a PNAS, including possible measurement platforms for the sensing part, possible modalities for the acting part, and examples of potential target groups is provided by Adams et al [17].

Development of a PNAS and Application in 2 Use Cases

In this paper, we have described the rationale behind the design choices made in developing our PNAS. This PNAS was developed as part of the Public Private Partnership Personalized Nutrition and Health, in which the Netherlands Organisation for Applied Scientific Research and Wageningen University and Research work together with private parties [36]. We aimed at developing a science based, dynamic PNAS that could be used in different target groups. To test the PNAS, 2 use cases were defined, one aiming at consumers with premetabolic syndrome motivated to change their diets to enhance their health (ie, highly motivated consumers; n=37) and the other aiming at consumers with a low socioeconomic status (n=96). The PNAS had to have a generic backbone but be able to handle different sets of input and output parameters. A digitalized PNAS that was suitable for use in these 2 use cases was developed and tested using 2 human studies [37,38].

This paper discusses the 3 generic components in PNASs; sensing, reasoning, and acting in general; and the design choices that were made for sensing, reasoning, and acting for our PNAS in the 2 use cases. First, we expand on the possible input parameters that can be used for sensing, including their caveats. Regarding reasoning, we will discuss how evidence-based food-health relations can be incorporated into a digital system and about the modeling

strategies that we used. Regarding acting, the focus is on communication of feedback (health and dietary status) and advice (dietary recommendations), and the use of behavior change techniques for activating consumers.

SENSING—PERSONAL DATA

Overview

When the main goal and target group of the PNAS are clear, the first step in the designing process is to decide on input or *sensing* parameters that can and should be included. There is a wide variety of possible parameters, including clinical measures, behavior, well-being, genetics, personal preferences, and so on [15]. Broadly, 2 categories of relevant data for personalization can be distinguished, namely, biological characteristics and data related to current behavior, preferences, barriers, and objectives [16]. To decide which sensing parameters to include in your PNAS, decisions need to be made about the scope of your system, for example, what aspects of health are relevant; which measurements are feasible; and what parameters need to be included to measure the success of your PNAS, for instance, in improving the health status or well-being of consumers [17].

For our PNAS, we decided to include both biological characteristics or *health parameters* and parameters related to current lifestyle behavior, which are further described in the following sections.

Health Parameters

To decide which health parameters to include in your system, it is important to consider what aspects of health are influenced by nutrition and how these can be measured. The concept of health used to be defined as a state of complete mental, physical, and social well-being [39]. However, currently, a more holistic approach is accepted, in which there is also a role for an individual's ability to cope with daily challenges [40]. The physical dimension of health, represented by the body and its overall functionality, covers a broad scope ranging from the absence of disease to the level of physical fitness. Classical physical health in a pharmacological or clinical setting is determined by the *phenotype*. The phenotype is often assessed by benchmarking anthropometric measurements and single overnight fasting plasma biomarkers against cutoff values that represent either a *healthy* or *compromised* status. Currently, health is considered as the body's ability to adapt to (changing) circumstances, while remaining within homeostatic boundaries [40]. This definition calls for alternative assessment methods that operationalize health by capturing the body's systemic response to (challenging) circumstances, instead of a single measurement such as fasting glucose [41]. When only clinical cutoffs are considered, subtle changes in overall health status may be overlooked. Therefore, integration of multiple measured biomarkers or phenotypic traits is key. For this purpose, a so-called health space model can be used, which combines multiple

biomarkers into a single score using multivariate statistical methods and data from reference populations [42,43].

The first step for incorporating health in a PNAS is to determine which phenotypic health parameters provide a good representation of the health status of a person and may provide the opportunity for personalized advice. In the simplest sense, parameters such as sex, age, and anthropometrics can be used, but often, more specific, and clinical measurements (i.e., plasma biochemical markers and vitals) and genotypic data are included to provide a more holistic overview of health. All measurements should be accurate, valid, and preferably relatively easy to obtain.

In our system, basic characteristics such as age and sex were combined with easy-to-measure anthropometrics and vitals such as body weight, blood pressure, body length, and waist circumference. Depending on the target population and the setting of the investigation, the set of measurements was either extended or reduced. One of our studies was performed with highly motivated consumers in a health care setting. Therefore, participants could be easily called to the clinic, which allowed for more extensive anthropometric measurements (e.g., fat percentage) and collection of blood samples for measuring plasma biomarkers (high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, glucose, and triglycerides and a nutrient profile). The other study with consumers with low socioeconomic status was set in a supermarket, which asks for easy-to-perform measurements with direct readouts. In such a setting, do-it-yourself measurements can be applied, such as body weight scales, blood pressure meters, and handheld devices for plasma biomarkers. In addition, wearables and apps could provide a good solution for assessment in a more do-it-yourself setting but were not part of our studies. The measurements to be included in a PNAS are also dependent on the target group. Highly motivated individuals were more willing to accept blood sampling [37] to be able to receive more detailed personal advice, as compared with those with low socioeconomic status who were less interested in nutrition-related solutions for health [38].

Lifestyle Behavior Parameters

In principle, a complete set of health parameters only, with sufficiently accurate values, could suffice in providing a personalized advice. However, in addition to the physical dimension of health, lifestyle, mental, and socioenvironmental factors influence health status, for example, food intake, physical exercise, stress, physical environment, and social support networks. Knowledge about an individual's current lifestyle will have added value in several ways. First, the set of health parameters is not sufficiently rich to cover all required aspects. Second, relations between lifestyle behavior and health status are not fully known, and this for instance limits the number of nutrients, foods, or food groups for which recommendations can be formulated [13]. Providing personalized recommendations relative to current food intake behavior can help to fill these gaps and enrich the personalized advice; however, the

recommendations themselves will be based on population-based cutoff values. Third, to some extent, current lifestyle behavior can also serve as a proxy for health status [44]. Finally, integrating current lifestyle behavior into personalized advice could increase the relevance of recommendations to match individuals' current behavior, and their habits and preferences, for instance, current physical activity patterns, can be incorporated [18]. Overall, two main approaches can be distinguished for the measurement of lifestyle behavior, namely (1) monitoring current lifestyle and (2) self-reporting on lifestyle behavior [45,46]. Monitoring can be performed using sensors and mobile apps, such as an activity tracker or a food diary app. Self-reporting mostly relies on questionnaires, which vary in the level of obtained detail and validity.

In our system, in terms of lifestyle, we focused on dietary intake. For measuring dietary intake over a period, several self-reporting measurement methods are available, including (1) food frequency questionnaires, which are commonly used to provide a quantitative measure of nutrient level; (2) food diaries or dietary recalls, which provide a quantitative output on nutrient level and product level; and (3) healthy eating indexes, which provide a more qualitative output in terms of overall healthiness of the diet [47-49]. However, these conventional tools for measuring dietary behavior have major limitations. They are subject to overreporting and underreporting, dependent on the willingness of a user to log their dietary intake, and dependent on the quality and details of the underlying food composition databases [47-49]. As an alternative approach, nutrient profiling in blood could be considered to capture dietary intake. This would include plasma levels of specific vitamins and minerals or metabolites as a proxy for dietary status [50,51]. In addition, a few biomarkers that can reflect dietary intake on a food group level exist, for example, alkylresorcinols for whole grain intake, lipid profiling for fish intake, and a combination of carotenoids and vitamins for fruit and vegetable intake [52,53]. Unfortunately, most of these biomarker levels reflect long-term dietary behavior rather than short-term food intake; in contrast, many metabolites have a short half-life and thus are not representative of habitual intake [50]. In addition, currently, biomarkers do not provide a complete picture of an individual's dietary intake. However, combining biomarkers with more *classical approaches* such as diaries and questionnaires may result in a more accurate assessment of dietary intake [27]. Another approach to assess dietary intake is to use a diet quality index to assess adherence to a specific dietary pattern, such as the Healthy Eating Index and the Mediterranean Diet Adherence Screener [54,55]. Such diet quality indexes are based on population-based dietary guidelines and provide insight into the overall diet quality and conformance of specific food groups that are key to a healthy diet. In addition, combinations of dietary assessment methods can be used.

As our studies were set in the Netherlands, for our system, we used the Dutch Healthy Eating Index (DHEI) questionnaire. The DHEI includes a set of 15 categories or *food groups*, consists of a relatively simple list of questions that can be answered in a short time frame, and results in a score ranging from 0 to 10 for the 15 food groups and a total diet score [56,57]. The reason for using this dietary assessment method is that we are not very interested

in obtaining the exact intake of macronutrients and micronutrients by individuals but merely in whether individuals comply with dietary guidelines at a food group level as a first step toward personalization. Using food groups for personalized advice instead of nutrients has several advantages: (1) focusing on food groups is more consistent with the shift in the Dutch dietary guidelines from single nutrients to food groups [58]; (2) both evidence-based relations between food groups and health parameters and between nutrients and health parameters can be incorporated in the system, using specific nutrients to further fine-tune the advice [59,60]; and (3) feedback and advice are easily applicable as consumers do not have to identify which foods are high in the recommended nutrients themselves. The disadvantage of using DHEI is that no information on the consumption of specific food products or the amount of macronutrients and micronutrients consumed can be obtained [57]. In addition, the DHEI provides output on a qualitative level, not quantitative; for instance, the DHEI does not provide insight into the exact amount of vegetables consumed (in grams). The DHEI is based on population-based dietary guidelines and can be used for distinguishing between categories ranging from healthy to unhealthy dietary behaviors for the included food groups. Such a subdivision can be used for personalizing dietary recommendations based on current dietary intake patterns. To further personalize the recommendations, this output can be combined with other parameters, such as health status markers, as described in the previous paragraph, which we applied in our PNAS.

REASONING—ADVICE MODEL

Overview

From the abovementioned arguments, it follows that 3 basic design choices must be made when developing digital systems for personal dietary advice:

- First, the health condition of an individual should be used as the actual variable to control. Health parameters are monitored, and their values are used to decide which aspect of dietary intake should be focused on [16,27]. This requires a model that maps health parameter values to nutrients, foods, or food categories that need attention. This model should be based on science-based relations between dietary intake and health impact [17].
- Second, current individual food intake should be considered as a starting point for an individual path toward healthy intake, rather than directly pointing to the optimal diet. Eating patterns cannot be changed at will; habits are difficult to change [61]. Therefore, we do not assess products in terms of *healthy or not healthy for a representative population* but analyze eating habits in terms of deficiencies or gaps with respect to the ideal situation [62]. For our system, we decided that measuring food intake at the category level was sufficient.

- Third, in principle, personal preference, motivation, and situation must be considered to ensure compliance with the generated advice [18]. In this study, this was limited to asking consumers to self-select which food category to focus on and to formulate implementation intentions for these, with the latter being a behavior change technique facilitating the communication for behavior change (refer to the *Behavior Change Techniques* section).

These design choices give rise to 2 questions. How can we create a software-based model that generates a personal advice, and how can we combine food intake data with health data in this model? In the following sections, we address the modeling approaches that we used for our PNAS, knowledge acquisition as a basis for an expert-driven model and composing personalized advice in a flexible manner.

Modeling Approach

For creating a model that links the observed health variables (such as blood pressure, LDL cholesterol level, and BMI) to food categories that need attention, ideally, we start from scientific publications and reports. However, constructing software models from scientific papers is a complicated and time-consuming process. In practice, we assume that dietary professionals already have operationalized this knowledge. For our system, we have applied knowledge acquisition methods from information science to develop the required software models. We consulted nutrition experts to informally describe the heuristics they use in practice in the form of, for example, a text file or a spreadsheet. They also provide pointers to the underlying scientific evidence. This process of *mining* expert knowledge [63] results in many knowledge rules. These rules can be expressed as decision trees or, more flexibly, as logical knowledge rules. However, for our system, we have selected Bayesian Belief Networks (BBNs) to express the relation between the observed health parameters and suggested changes in diet (ie, advice).

BBN is a probabilistic model that represents a set of variables and their conditional dependencies using a directed graph. The advantage of this approach is that tools are available to start with an initial qualitative influence diagram and then progressively add quantitative details. The experts can then evaluate the overall effect of the combined heuristics they provided by running the reasoning capabilities of the network and verify the predictions made.

In our case, the network represents the probabilistic relationships between health variables (input) and advice variables (output). Each of the parameters in our model has several discrete values (states); for example, for the input parameter systolic blood pressure, we used the values, *90 to 110*, *110 to 129*, and *130 to 250*. Each state in the outputs refers to a text fragment that is provided to the consumer, for example, “no_advice,” “high-blood-pressure_eat_sufficient_vegetables,” and “enrich_with_nuts.” The links between the input and output parameters express the probability that the state of one parameter leads to a certain

state of the other parameter, expressed as percentage. In our current model, we assume that if each of the input parameters is in a single state (i.e., this state has a probability of 100% and the other has 0%), then each of the output parameters also is in a single state. However, the strength of BBNs is that they permit a distribution of probabilities over multiple states, allowing uncertainty in the inputs and outputs. For example, if BMI is unknown and the probability of high waist circumference is 45%, there is a 10% chance that no advice is needed regarding vegetable intake. However, determining these probability values manually is very difficult and considered as future research.

An important advantage of the BBN is the fact that it is possible to combine explicit expert heuristics with additional observational data as knowledge sources to compute probability values or even create the network itself. Once we have collected enough data from observations regarding how dietary advice parameters have influenced the health parameters, it is possible to *train* the model with these data and automatically adapt the probability tables. In this study, sufficient data were not collected to perform this next step.

Knowledge Acquisition

The process of knowledge acquisition involves several rounds of interviews with dietary experts and systematic record keeping, in which domain experts and knowledge engineers work together. Such a process often reveals hidden assumptions, differences in terminology, and controversies among experts. Overall, 2 methods can be used to resolve such issues: *confrontation among experts* and *relating to underlying science.*

A typical issue in knowledge acquisition that often raises debate among experts arises from conflicting classifications. For example, the general Dutch guidelines use the category, *bread*, for a range of products and provide cutoff values for healthy consumption. However, some food intake apps use the category, *whole grain product*, for different types of products such as bread, pasta, and rice. How should we then classify *whole grain bread*? This type of semantic discussion among experts can often be resolved by applying appropriate modeling practices. In this case, *bread* can be used as a *class,* defining a group of products that use similar ingredients and preparation methods. In contrast, the concept, *whole grain*, indicates that a product is produced from whole grains, which should be expressed by the *property*, "is_produced_from," rather than by defining a distinct *class*, *whole grain products*. In this way, *whole grain bread* is a type of *bread*, with property, "is_produced_from = whole_grain." Another interesting but confusing category is the notion of *unhealthy product* in the context of personalized advice. By assigning food products as instances of this predefined class, we assume that these products are unhealthy for anyone in any situation. This contradicts with the idea that what is healthy depends on the individual, their entire dietary pattern, and their context and should therefore be modeled as a (derived) *property* rather than a *class*.

For the second approach to solving knowledge conflicts, that is, *relating to underlying science*, the experts were asked to select relevant publications to support the heuristics they

expressed. This is certainly not a straightforward task. In food-health research, scientific studies often use *nutritional values* as input variables, as these basic metabolic and physiologic mechanisms are often known. However, relations expressing the impact of entire foods and dietary patterns on health are also needed, as these take nutrients in a food matrix and interactions between foods into account. These 2 different approaches (nutritional values vs food categories and diets) also need to be reflected in the knowledge rules that are used in individual advice. In our study, we have chosen to stay at the level of food categories and have the experts decide on how nutrient-level evidence is incorporated. For example, for some categories, we know that they are typically high in a particular nutrient (e.g., omega-3 fatty acids in fish). In this case, we can use the evidence at the nutrient level for the associated food category. In addition, we have used nutrient-health relations to elaborate the final advisory texts. For example, we recommend species of fruit that are high in fiber for people with high blood pressure, as fiber can help to reduce blood pressure.

Finally, the experts also needed to decide whether the conditions under which the underlying studies were originally performed can be generalized to our system and target groups. As our system is developed for use in the Netherlands, for instance, evidence from meta-analysis on food-health relations in the Asian population was excluded [64]. In addition, the level of evidence and quality of the research should be considered, for instance, using the Grading of Recommendations, Assessment, Development, and Evaluations method [65]. Regarding our knowledge rules, we used evidence as given by the Dutch Health Council, which applies a thorough but time-consuming literature review process to translate observed health effects in cohort studies to generalized rules for the impact of food categories on health, as a basis. We extended this basic set with rules derived from more recent literature and additional publications covering health parameters that were not within the scope of the Dutch Health Council (eg, glucose, triglycerides, and HDL cholesterol levels and waist circumference). An example of the latter is a meta-analysis showing the beneficial effects of whole grain consumption on blood glucose levels and risk of type 2 diabetes [66-68]. The additional knowledge rules that were added to our system also include food-health relations as accepted for health claims by the European Food Safety Authority, based on evidence from a recent meta-analysis.

Composing the Advice

In this section, we explain in more detail how we algorithmically combined health parameters and food intake measurements to create a composite personal advice.

First, the input nodes of BBN were defined as the amount of intake for the categories used in the DHEI questionnaire (i.e., vegetables, fruit, whole grain products, salt, fish, dairy, sugar-containing beverages, butter, nuts, coffee, alcohol, and unhealthy snacks) and the values of several health parameters (i.e., BMI, waist circumference, diastolic and systolic blood pressure, glucose, triglycerides, LDL, HDL, carotenoids, alkylresorcinols, and omega-3 fatty

acids index). Second, the output nodes for the network were then broken down into separate advice texts at 4 *levels* (Textbox 1).

Textbox 1. *The 4 advice levels in our personalized nutrition advice system.*

Advice levels

- The first level provides feedback about the current food intake—does a consumer comply with the dietary guidelines for a food group? For example, the advice text could state "You eat little fish."
- The second level indicates whether the consumer's health status directs attention to a specific food category. For example, "Because of your high blood glucose level it is very important for you to consume sufficient dietary fiber."
- The third level motivates consumers to increase, maintain, or decrease their current dietary intake, based on the output of the first 2 levels. For example, "Try to eat more fiber-rich products."
- The fourth level provides both general and personalized practical tips. The first tip is linked to the current dietary intake and provides the suggestion to increase or decrease current intake (if not meeting the guidelines) or to increase variation (if meeting the guidelines). The second tip contains practical advice for a consumer to improve their health status. For example, "Choose oatmeal for breakfast, and add a full tablespoon of flaxseed to add extra fiber."

Then, BBN connects the input nodes to the output nodes, following the heuristics provided by the food experts. This is illustrated in Figure 1. In several iterations, we adjusted the transition probabilities between the nodes to verify and improve the impact of the collective input values on the outcome of the model. In this way, we achieved consensus among the experts based on their professional knowledge and experience.

ACT—COMMUNICATION FOR BEHAVIOR CHANGE

Overview

The final step in the process of providing personalized advice is communicating the personalized advice to the consumer. The way in which the advice is provided to the consumer is critical, as studies have shown that individuals pay more attention to recommendations that are perceived as more relevant to them [69]. Several approaches can be used to increase perceived relevance of the advice by the consumer. In our PNAS and studies, the following 4 approaches for personalized communication were applied:

- Provide feedback about consumer's current lifestyle and health status to confront them with their actual behavior or health status, motivate them to act, and monitor their improvements over time.

- Increase the relevance and applicability of the advice itself by ensuring that it fits a consumer's preferences, for example, by adjusting the framing and format of the advice to the personal characteristics of the receiver.
- Determine an appropriate source—the source of the advice plays an important role in determining the credibility of the advice.
- Apply behavior change techniques to increase involvement and compliance of the consumer with the advice, for instance, by using implementation intentions or if-then plans to specify when, where, and how one will achieve a certain behavior [70].

These 4 approaches are further discussed in the following sections.

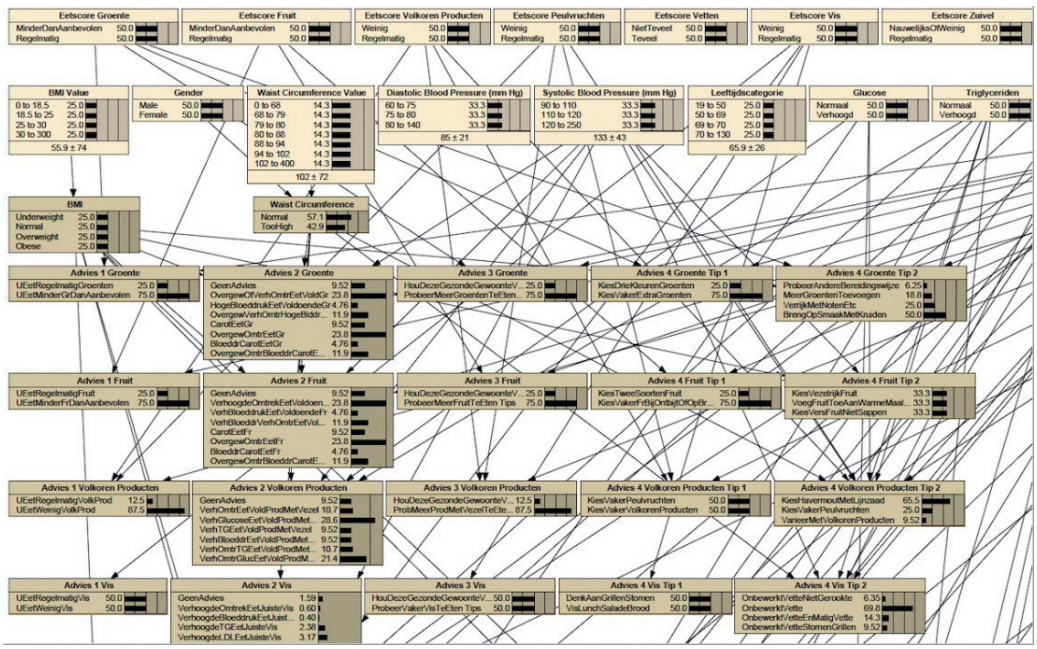

Figure 1. *Part of the Bayesian Belief Network. The first and second rows contain input values. The first row contains intake values for the food categories from the Dutch Healthy Eating Index questionnaire. The second row contains values for the included health measurements. The third row includes some intermediate parameters, that is, BMI and waist circumference (qualified values). The lower rows show the 4 levels of advice, each row presenting a food category. Note that all values are divided into discrete ranges.*

Feedback About Health Status and Behavior

In both studies in which we applied our PNAS, we not only provided personalized advice to the participants but also feedback about their current health and dietary status. In the study with highly motivated consumers, feedback and advice were provided via a web-based portal and discussed during a telephone consultation with a dietician. Follow-up was performed via email. In the study with consumers with low socioeconomic status, the feedback and advice

were provided via a report that was sent to participants via email. As consumers should not be overwhelmed by the feedback, long lists of data that consumers cannot interpret or do not know how to act on should be avoided. To make feedback about health status more easily understandable by consumers, several strategies can be applied, such as color coding or composite scores that give an overall view of the health status or benchmarking personal data to the general population or peer groups (for an example, refer to the study by Morrow et al [71]).

In our PNAS, we provided consumers with their individual scores on relatively well-known single biomarker values (eg, blood pressure, body weight, and cholesterol) and plotted them against generally accepted healthy ranges. Color coding was used to indicate whether the individual values were within the healthy range, borderline, or outside the healthy range (Figure 2). This strategy has been shown to increase understanding of health data, especially for people with low numeracy skills [72].

In addition, in the study with highly motivated consumers, we provided health status feedback by integrating the outcomes of all markers into a composite score for overall *metabolic health* (Figure 3). To calculate the metabolic health score, a so-called health space model was developed (refer to the *Sensing—Personalized Data* section). Visualizations of such a metabolic health score may provide a valuable tool in communicating overall health status to individuals and can be used to show how an individual scores as compared with peers or to monitor changes in health over time [15,73]. This may make it easy for individuals to see their progress over time, as compared with having to weigh changes in various health parameters themselves.

Furthermore, in the study with consumers with low socioeconomic status, feedback about dietary intake was provided by means of stars per food category (eg, vegetables, whole grains, and unhealthy snacks), which reflected a score on a scale from 1 to 10 (Multimedia Appendix 1). Visualizing these scores helped to improve understanding in a group with low socioeconomic status [38]. Nevertheless, although we tried to make it simple, especially in the study with consumers with low socioeconomic status, some individuals indicated in the evaluation of the study that the feedback was sometimes difficult to understand (Figure 2 and Multimedia Appendix 1). This outcome indicates how difficult it is to provide the correct format of feedback and how concisely these aspects must be adjusted to the target group. As our studies were performed with 2 different target groups and the provided feedback and advice formats were not identical between these studies, no firm conclusions can be drawn on how to best differentiate in communicating feedback between these target groups. Future studies including various target groups that are exposed to various types of feedback and advice should be performed to further investigate how feedback can best be communicated to (different types of) consumers.

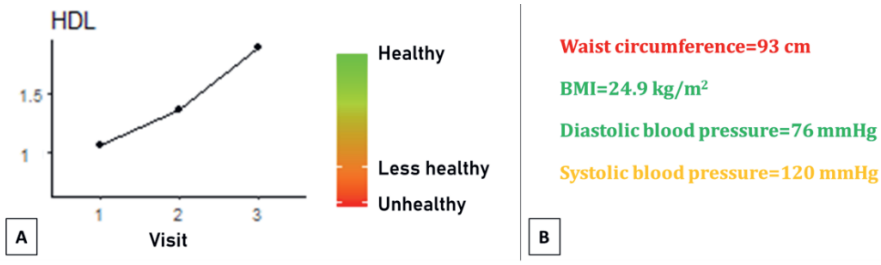

Figure 2. *Examples of color-coded feedback about individual biomarker values. (A) Graphical representation as used in the study with highly motivated consumers; (B) textual representation as used in the study with consumers with low socioeconomic status. HDL: high-density lipoprotein.*

Figure 3. *Example of composite score for overall metabolic health, as provided to participants in the study with highly motivated consumers.*

Relevance and Applicability of Personalized Advice

Motivation to receive personalized advice and engagement in a personalized dietary program are essential for the success of a PNAS. To increase this motivation, personalized recommendations should connect to the most important goals that consumers may have regarding receiving personalized dietary advice. The results of a consumer survey conducted within the Personalized Nutrition and Health program revealed that having a clear health goal (eg, losing weight) is a more important determinant of success than *just obtaining insight* into one's dietary pattern and obtaining possibilities for improvement [74]. In addition, a difference was observed between age groups—older people were relatively more interested in receiving advice regarding specific health solutions (i.e., losing weight, avoiding illness, or improving specific health aspects), whereas young people were more holistically interested in improving their lifestyle (i.e., feeling fitter, gaining more energy, or developing healthy eating habits) by means of personalized recommendations.

The applicability of the advice can be increased by the way in which the advice is formulated. As indicated previously, in the studies, the advice text contained practical tips (Textbox 2). Evaluation of the studies indicated that the provided personalized advice was perceived as helpful to improve diet, easy to understand, useful, and fun. More importantly, the groups of

participants that received personalized advice better saw the link between their diet scores and showed greater improvement in dietary habits than the group of participants that did not receive personalized advice.

Textbox 2. *Example of advice text along with practical tips on how to implement the advice (translated from the original Dutch text).*

Example of advice text and practical tips

- You eat few whole grain products.
- Because of your increased waist circumference, it is extra important for you to eat enough dietary fiber. Try to eat more products rich in dietary fiber. Tips for eating more dietary fiber:
  - Try to choose whole meal bread more often and use whole meal products in the evening meal such as whole meal pasta, potatoes, and brown rice.
  - Try to opt for legumes more often by adding lentils, chickpeas or kidney beans in a salad or soup, or eat a slice of whole meal bread with hummus.

Source of Personalized Advice

The source of personalized advice influences perceived trustworthiness, relevance, and adherence. Previous studies show that a dietician is perceived as one of the most suitable providers of personalized nutrition advice [75]. In our study with *highly motivated consumers with premetabolic syndrome*, the advice was provided by a dietician, which was perceived as positive. However, advice obtained via telephone consultation was appreciated higher than that obtained via email. In consultation with the dietician, the advice generated by the model was discussed and further aligned to individual needs and capabilities, resulting in a behavior change strategy (e.g., adjusting portion sizes or replacement of products within or outside the food category).

Behavior Change Techniques

An important way to realize behavior change is through the application of behavior change techniques that are proven to be effective [76]. A behavior change technique is a strategy that helps an individual to change their behavior to promote better health. Michie et al [77] developed a hierarchically ordered taxonomy of 93 distinct behavior change techniques with labels, definitions, and examples. For our studies, we used one of these techniques, that is, implementation intentions, or if-then plans to specify when, where, and how one will achieve a certain behavior [70]. Previous research findings show that implementation intentions are more effective when consumers can formulate their own implementation intentions [78-80]. In addition, it is suggested that consumers can only handle a few behavior changes or implementation intentions at a time [78,81]. This could make implementation intentions a perfect tool to implement personalized advice. For example, in a pilot study among older consumers, participants were instructed to formulate implementation intentions in which they described how they planned to apply at least 2 of the received personalized advice [24]. More

specifically, participants had to explicitly indicate at which time of the day and in which situation they were planning to replace an unhealthy product that they reported in their 3-day food diary with a healthy product. However, as the results of this pilot study show that compliance with the personalized advice did not improve throughout the study period, replacing one food with a healthy alternative is likely to be insufficient. In our personalized advice system, we used free text to formulate the implementation intentions instead of using predefined text fields. In one study, a dietician helped consumers with formulating these implementation intentions, whereas in the other study, implementation intentions were formulated together with the researcher in the supermarket. Future studies should determine how the effectiveness of implementation intentions can be further optimized and supported.

Ethics Approval

The study with highly motivated consumers was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Tilburg University (file number NL61382.028.17). For the study with consumers with low socioeconomic status, the ethics committee of Tilburg University (file number NW2017-42) determined that the study does not fall under the Medical Research Involving Human Subjects Act. All participants provided informed consent for inclusion before they participated in the studies.

DISCUSSION

Summary

In this paper, we described the rationale behind the design choices made while developing our PNAS using the *sense, reason, and act* principle. This PNAS was tested in 2 studies, 1 with *highly motivated consumers with pre-metabolic syndrome* and 1 with *consumers with a low socioeconomic status*. The reasoning engine, a BBN, was identical for both studies and could handle different combinations of input parameters. For the study with highly motivated consumers, the resulting feedback and advice were displayed in a web-based portal. For the study with consumers with low socioeconomic status, feedback and advice were provided via an automatically generated report that was sent to the participants via email.

Sensing

In terms of *sensing*, the main challenge is to decide which input parameters are relevant for your PNAS. The consumer burden of performing measurements should be weighed against their added value in providing a more personalized dietary recommendation. The main determinants in choosing measurement methods are their reliability, validity, responsiveness [82], and feasibility in a setting (e.g., do-it-yourself setting). Self-reporting can result in low data quality, irrespective of the method selected [83,84]. In contrast, the gold-standard

method, such as using double-labeled water for caloric intake [85], is not always feasible in a real-life setting. The measurement method that is most suitable (e.g., for measuring food intake) in a setting depends on multiple factors, such as the required level of detail (food patterns, food groups, or specific nutrients), available guidance when collecting the data, and measurement frequency. When using self-reporting, it is important to design short questionnaires to obtain information from individuals. For example, Demark-Wahnefried et al [86] showed that intervention participants found brief interim surveys that assessed specific behaviors more helpful than long, standardized surveys. In addition, technology-based tools such as those using additional food images can help to improve the data accuracy of self-reported dietary assessments [87,88]. Finally, one may also consider adding supplementary sources, such as purchase data or dietary intake markers.

For health monitoring, new technologies and do-it-yourself options are becoming available. Health can be monitored via different types of wearables and at-home assessment kits (pregnancy test and genetic testing). However, accuracy and validity of these measurement methods are not always guaranteed, especially in a do-it-yourself setting [89,90]. Collecting dried blood spots is possible in an at-home setting but requires high-quality blood spots and may be subject to undersampling or hematocrit bias or effect [91], and sufficient analysis capacity is required. The type of measurement that is acceptable also depends on the target group. Our studies showed that highly motivated individuals were more willing to accept blood sampling to receive more detailed personal advice [37] than individuals with low socioeconomic status who were not particularly interested in nutrition-related solutions for health [38].

The collected health data can also help to improve the algorithms underlying personalized advice. For instance, they can assist in identifying food-health relations at an individual level. The key is that the health information can be linked to nutritional recommendations. It can be argued that a single measurement is not sufficient, and that long-term monitoring and reassessment are required to track changes in dietary behavior and health effects. With this input, the advice to the individual can be continuously updated and fine-tuned.

When providing feedback about health status, the potential for health gain for the individual should be clear. For instance, the Wii fit regularly shows consumers the difference between their real age and their *Wii fit age*. In theory, this could be a meaningful score, but in practice, it has been proven invalid and unreliable [92]. The new definition of health calls for alternative assessment methods that observe the body's systemic response to variable circumstances instead of performing a single measurement, such as fasting glucose level [41]. This could be achieved by integrating multiple biomarkers or phenotypic traits into a single, understandable score that represents health [42]. In the future, other measurements could also be included (ie, mixed meal, exercise, or stress challenge tests [93]), but their added value for personalized nutrition and feasibility in practical conditions are still unclear.

In summary, regarding *sensing*, we recommend trying to find a good balance between the input parameters that you need to deliver the personalized dietary advice and the burden that you pose on your user—match the necessary parameters to the intended purpose of your PNAS and make a distinction between *must have* parameters and *nice to have* parameters. In addition, also in terms of repeated measurements, each time you ask a user for personal data, think about the value that you can provide them in return.

Reasoning

Regarding *reasoning*, we discussed the use of a BBN for representing food-health relations. This approach allows combining a knowledge-driven approach with a data-driven approach; at first, a qualitative network can be created with nutritional experts, which can then be enhanced with observational data. However, the latter requires sufficiently large data sets. Therefore, in small studies, other knowledge-based modeling approaches may be more suitable, such as decision trees or system dynamics models [15]. The main challenge in such approaches is to determine the strength and reliability of the food-health relations. Ideally, we would assign a standardized *level of evidence* marker for each knowledge rule. With such a parameter, each user of a knowledge rule could decide which level of evidence is acceptable in a particular use case [50]. An advantage of expert-driven models is that they are transparent and can be based on biologically plausible mechanisms [94]. Advantages of a data-driven approach are that data from many different markers can be analyzed simultaneously, for instance, using machine learning techniques [13]. Disadvantages are that the interpretability of such models and algorithms may be low and that these methods are at risk of sampling and selection bias [17]. Hybrid models that combine both approaches could provide the best of both worlds. In any case, the developed models and PNAS systems should be validated using human intervention studies, published in peer-reviewed journals [17].

To summarize, for *reasoning*, the main message is to carefully consider whether a data-driven, knowledge-driven, or hybrid model is best suited for the intended PNAS. In addition, we recommend to not build your system around a particular technology or software solution. Technologies become obsolete, and it is risky to rely on a single software solution. Instead, think about the basic algorithm or knowledge rules that you aim for in your system and implement them in a modular architecture (ie, based on web services that can be maintained independently). In addition, ensure that you have a clear understanding of the role of the data that you build your system around and have a clear data security plan.

Acting

For *acting*, we discussed the importance of proper communication of feedback and advice to consumers and the use of behavior change techniques for activating consumers (eg, implementation plans). Note that, until now, little to no scientific research has been conducted to determine how a personalized nutrition advice should best be communicated to consumers [95]. This is a serious shortcoming, as studies show that the way in which message content

is processed and remembered greatly depends on how this information is delivered [96,97]. Relevant insights from social psychology and marketing literature can be useful to formulate advice for consumers that is effective in helping them to choose and maintain an optimal personalized diet.

In developing our PNAS, we also considered the format of the feedback and advice provided. For example, to make feedback about health status more easily understandable, color coding or composite scores were used. At this point, composite scores mostly represent a specific aspect of health, such as metabolic health, muscle health, or inflammation status [24,98]. Integration of all markers in a single health score could be even more effective. Other approaches that integrate multiple health aspects in a single visualization are already available, but none of these provide a single health score [73,99]. The influence of composite health scores on consumer understanding, motivation, and behavior change is not sufficiently known yet.

The advice we presented in the studies contained practical tips, making the advice more easily applicable in daily life. Ideally, the framing and format of such advice is adjusted to personal characteristics of the receiver of the advice. In one of our studies, this was accomplished by a dietician, who adapted the advice to a practical application for the participant. However, ideally, a digital advice system also takes these personal needs into account. This may involve tailoring the framing and timing of the advice to specific personality types [100]. Previous studies have shown that both an entirely digital approach and a digital approach combined with coaching resulted in healthy dietary behavior; however, user engagement was high in the combined approach [101].

In addition, we asked participants to formulate implementation intentions. Future studies should examine other behavior change techniques also. As an extended list of techniques exist (eg, as specified by Michie et al [76]) that could potentially add to the effectiveness of personalized dietary advice, we recommend future studies to incorporate a broad range of behavior change techniques and identify potential synergies by combining different behavior change techniques. For example, Social Cognitive Theory [102] provides insight into how individuals regulate their behavior to achieve goals that can be maintained over time. For example, self-efficacy, defined as the extent to which one believes in their own ability to reach a certain goal, influences reaching that goal [102]. However, self-efficacy is difficult to influence, also when using personalized advice, as shown by Doets et al [24]. They found that self-efficacy decreased during the study in both the intervention group that received personalized nutrition advice and the control group that received generic dietary advice. This reduced self-efficacy could also be a result of the fact that during the study, participants were confronted with their (unhealthy) diet, which may lead to lack of confidence in someone's ability to succeed [103]. In their meta-analysis, Prestwich et al [104] revealed that emotional stress could undermine a positive effect on self-efficacy. Interventions that incorporate techniques that help to manage this stress were more successful in raising dietary self-efficacy

than interventions that do not. Therefore, we recommend future studies in the context of personalized nutrition advice to also include some type of stress management technique as part of the intervention.

To summarize, regarding *acting*, it is important to tailor the communication of the advice to the target group, in terms of format, choice of words, and complexity. Moreover, use different behavior change techniques and choose the technique that best meets the needs of the target group.

Conclusions

To set up or further develop a personalized advice system considering a sense, reason, and act approach is of value. It provides guidance and structure for making design choices for developing a (partly) digitalized solution. Besides the type of personal dietary advice and the mode through which it is generated, the communication of the advice and appropriate behavior change techniques should be considered, as this will determine the level of consumer adherence. This paper shows the vastness of choice options in designing personalized advice systems. All these choices will eventually influence the functionality, complexity, consumer appreciation, and effectiveness in achieving the desired health outcomes of such systems.

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9

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.

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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LAY SUMMARY IN DUTCH

Niet-overdraagbare ziekten, zoals hart- en vaatziekten, diabetes en kanker, veroorzaakten in 2019 wereldwijd meer dan 40 miljoen sterfgevallen (GBD 2019). Samen zorgde dit voor meer dan 70% van de totale sterfte. Een groot deel van deze sterfgevallen had voorkomen kunnen worden door effectieve volksgezondheidsinterventies, leefstijlinterventies of goede gezondheidszorg. Vooral ongezonde voeding, te weinig bewegen, alcoholmisbruik en roken spelen een belangrijke rol bij het ontstaan en de progressie van deze ziekten. Een gezonde levensstijl kan het risico op diabetes type 2, hart- en vaatziekten en sterfte aanzienlijk verlagen. Echter, veel volwassenen voldoen niet aan de richtlijnen voor gezonde voeding en lichaamsbeweging.

Verschillende onderzoeken hebben aangetoond dat een gezonde leefstijl de incidentie van diabetes kan verminderen, waarbij zowel gewichtsverlies als lichaamsbeweging een rol spelen. Ook gezonde voeding speelt een belangrijke rol in het voorkomen en behandelen van diabetes type 2. Dieetpatronen zoals het Mediterrane dieet of het Amerikaanse DASH-dieet kunnen bijvoorbeeld het risico op diabetes type 2 verminderen. Ook hebben verschillende voedingspatronen en lichamelijke activiteit gunstige effecten op het beheersen van de bloedsuikerspiegel bij mensen met diabetes type 2.

Er zijn echter grote verschillen tussen mensen in de effecten van leefstijlinterventies. Dit komt onder andere door verschillen in leefstijl, voorkeuren, genetische kenmerken en fysiologische reacties tussen individuen. Daarom is het belangrijk om leefstijlinterventies te personaliseren op basis van individuele kenmerken en doelen. Dit kan onder meer worden bereikt door gebruik te maken van gepersonaliseerde voeding- en beweegadviezen, waarbij de response van een individu op bijvoorbeeld voeding of bewegen wordt gemeten en wordt gebruikt voor gepersonaliseerde feedback en advies.

Diabetes type 2 wordt steeds meer erkend als een heterogene ziekte, waarbij individuen verschillen in glucosehuishouding, de mate van insulineresistentie en ziekteprogressie. Het identificeren van verschillende subtypen van diabetes kan helpen bij het personaliseren van de behandeling. Door de reactie op leefstijlinterventies van individuen te begrijpen en te meten, kunnen deze interventies effectiever worden gemaakt. Het gebruik van continue glucosemonitoring kan bijvoorbeeld helpen bij het bieden van real-time feedback en het optimaliseren van de glucosespiegels bij mensen met diabetes.

Om gepersonaliseerde leefstijlinterventies toe te kunnen passen, is goed wetenschappelijk bewijs voor de effecten van deze interventies van belang. Daarnaast moeten gepersonaliseerde leefstijlinterventies bij voorkeur ook worden onderzocht in het dagelijks leven van eindgebruikers om de haalbaarheid en effectiviteit van deze interventies goed te kunnen beoordelen. Door de opkomst van wearables en continue glucosemonitors wordt het steeds makkelijker om in het dagelijks leven onderzoeksgegevens te verzamelen, maar ook om gepersonaliseerde adviezen aan te passen aan de veranderende leefstijl, context of gezondheid van individuen.

Dit proefschrift beschrijft onderzoek naar de effecten van gepersonaliseerde leefstijlinterventies voor de preventie en behandeling van diabetes type 2. Er zijn twee studies uitgevoerd naar het effect van een gepersonaliseerde leefstijlinterventie op de gezondheid bij een gezonde populatie. Eén van deze studies werd uitgevoerd bij gezonde ouderen, een

andere bij werknemers. In beide studies werd er op basis van een aantal metingen in het bloed, lichaamssamenstelling, huidig leefstijlgedrag, persoonlijke voorkeuren en aantal specifieke genetische variaties een persoonlijk leefstijladvies gegeven. Dit leefstijladvies bestond in de studie met ouderen uit een tekstueel advies voor verschillende voedingsgroepen en bewegen, waarin met stoplichtkleuren werd aangegeven waar de belangrijkste verbeterpunten zaten. In dit advies stonden ook gerichte tips om de leefstijl te verbeteren. De deelnemers in dit onderzoek werden aangemoedigd om persoonlijke doelen te stellen voor minimaal één van de verbeterpunten. In de studie met werknemers werden de deelnemers ingedeeld in een aantal subgroepen die bepaalden hoeveel koolhydraten, eiwitten en vetten ze het beste konden eten. Daarnaast werden er ook adviezen gegeven voor micronutriënten en bewegen. Deelnemers werden tijdens het werk voorzien van maaltijden die aansluiten op hun persoonlijke advies. Daarnaast werden deelnemers door middel van motiverende gespreksvoering aangemoedigd om persoonlijke leefstijldoelen te stellen. De gepersonaliseerde interventies leidden tot betere naleving van dieetadviezen en verbeteringen in de gezondheid, zoals gewichtsverlies en een betere lichaamssamenstelling. Dit gebeurde zelfs zonder dat er in de interventies nadruk werd gelegd op caloriebeperking of gewichtsverlies. Wel leek uit beide studies dat de leefstijlinterventies het beste werken voor mensen die al een verminderde gezondheidsstatus hadden. Dit geeft inzicht in de potentie van gepersonaliseerde leefstijl voor het voorkomen van chronische ziekten zoals diabetes type 2.

Er werd in twee andere studies gekeken naar het effect van gepersonaliseerde leefstijlinterventies in de behandeling van diabetes type 2 in de eerstelijnszorg. Hierbij werd onderscheid gemaakt in verschillende subtypes van diabetes type 2, oftewel 'diabetypes'. Dit betekent dat de leefstijlinterventie op basis van een uitgebreide suikerwatertest en het afnemen van bloed beter kan worden afgestemd op de specifieke oorzaken van diabetes voor een individu. De persoonlijke adviezen werden gecombineerd met ondersteuning bij gedragsverandering, zoals feedback over gezondheid en het stellen van realistische doelen. Resultaten van deze studies suggereerden dat op maat gemaakte interventies effectiever kunnen zijn in het verbeteren van de glucosehuishouding en het behalen en behouden van gewichtsverlies dan de reguliere standaard aanpak in de zorg.

Verder onderzoek is nodig om de effecten van gepersonaliseerde leefstijlinterventies beter te begrijpen en om te bepalen wat de beste onderzoeksopzet is. Ook moeten we goed kijken naar de praktische haalbaarheid en waar de toegevoegde waarde van gepersonaliseerde adviezen zit voor individuen. Oftewel, ook in het ontwikkelen van een persoonlijke leefstijlinterventie is het belangrijk om goed na te denken over de doelgroep, haalbaarheid van bepaalde metingen, en de mogelijke effecten op leefstijl en gezondheid. Kortom, dit proefschrift laat zien dat gepersonaliseerde leefstijlinterventies veelbelovend zijn voor het voorkomen en behandelen van diabetes type 2, maar dat er nog meer onderzoek nodig is om deze interventies verder te optimaliseren en toe te passen in de praktijk.

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ABOUT THE AUTHOR

CURRICULUM VITAE

Iris Maria de Hoogh was born on 27 June 1986 in 's-Gravenzande, the Netherlands. In 2004, she completed secondary school at the 'ISW Gasthuislaan' in 's-Gravenzande with a biology and natural sciences based curriculum and a school research project on healthy nutrition. Hereafter, she started with the bachelor program Nutrition & Health at Wageningen University. During her bachelor program, she was board member of AIESEC Wageningen, a one-year full-time position. She was responsible for the outgoing internship program and managed a team of 5 persons. After having received her BSc degree in 2009 she enrolled in the Master program 'Nutrition & Health' with a specialization in 'Nutrition in Health and Disease'. She wrote her thesis on Sampling Designs in the Childhood Obesity Surveillance Initiative, which was commissioned by the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands, and the World Health Organization (WHO) Regional Office for Europe in Copenhagen, Denmark. She also followed the Master program 'Management, Economics and Consumer Studies' with a specialization in 'Marketing and Consumer studies'. She wrote her thesis on consumer attitudes towards the use of novel chemical and natural sweeteners in dairy products at Royal FrieslandCampina. Her internship was part of the REACH project: Renewed Efforts Against Child Hunger, a partnership project between the UN World Food Program (WFP), Food and Agricultural Organization (FAO), World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF).

After completing both master programs in 2011, she was shortly employed by the Recruitment and Communication department of Wageningen University. In 2012 she joined the two-year traineeship of the Netherlands Organization for Applied Scientific Research (TNO). Hereafter she continued working at TNO as a scientist. In 2019 she was admitted as a dual PhD candidate within the division of Internal Medicine at the Leiden University Medical Center, under supervision of Prof. Dr. Hanno Pijl. Dr. Suzan Wopereis, of the department of Microbiology and Systems Biology at TNO, was appointed as co-promotor. At TNO, and as part of her PhD trajectory, Iris was involved in the design, conduct, analysis and reporting of several human intervention studies on personalized lifestyle interventions in various target groups, including people with type 2 diabetes, elderly people and employees. Also, she was involved in setting up a public private partnership project on 'Using Continuous Glucose Monitoring and contextual data to increase insight in unhealthy glucose patters for individuals with type 2 diabetes' in which TNO cooperated with LUMC, Roche Diabetes Care B.V., Reinier Haga Medical Diagnostic Center and Ekomenu. In this PPP project she was the lead scientist for the human intervention study. As part of her work at TNO and for her PhD trajectory, she visited multiple international conferences and presented several abstracts. In 2017 she received the Young Investigator Award at the 14th Nutrigenomics conference. In 2022 she was awarded the publication prize by the Netherlands Association for the Study of Obesity (NASO). She is a board member of the Working Group 'dietary habits' ("WeVo), a network of nutrition, lifestyle and behavioral scientists. She is also a member of the NAV, the Dutch Academy for Nutrition Sciences.

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