BEYOND THE PLATE

MILANNE M.J. GALEKOP

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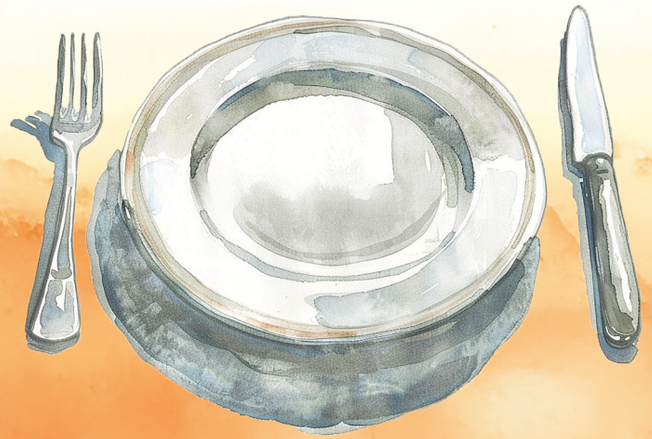
An early health technology assessment of the potential of personalized nutrition



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COLOPHON

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Beyond the Plate

An early health technology assessment of the potential of personalized nutrition

Voorbij het bord
Een vroege 'health technology assessment'
naar de potentie van gepersonaliseerde voeding

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

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born in IJsselstein, the Netherlands.

Erasmus University Rotterdam

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Prof.dr.ir. P.J.M. Weijs

Copromotor: Dr. W.K. Redekop

Just Do It

— Nike

CONTENTS

Chapter 1

General introduction

In 2019, the foremost global causes of death were dominated by ischemic heart disease (IHD), contributing to 16% of total deaths, followed by stroke at approximately 11% (1). Diabetes has recently entered the top 10 causes of death, showing a substantial 70% increase since 2000. Notably, diabetes witnessed the most significant surge in male deaths among the top 10, with an 80% rise since 2000 (1). Of the top 10 causes, seven were noncommunicable diseases (NCDs). There are several risk factors contributing to NCDs, such as tobacco use, physical inactivity, harmful use of alcohol, air pollution and unhealthy diets (2). While a comprehensive health strategy addressing multiple risk factors is optimal for preventing NCDs (3), prioritizing dietary improvements serves as a fundamental step. Establishing healthier diets not only forms the basis for overall health and well-being (4) but also addresses a well-known myth–that exercise alone cannot 'outrun a bad diet' (3). This underscores the important role of dietary improvement in preventing NCDs.

The association between diet and diet-related non-communicable diseases (NCDs) may involve intermediary factors such as high blood pressure, elevated blood lipids (e.g., high LDL-cholesterol and triglycerides), or pre-diabetes (4–8). These conditions, in turn, can stem from suboptimal diets (as a risk factor) or may be intermediated through overweight and obesity (9–11). Figure 1.1 illustrates the intricate relationship between various risk factors, leading to diverse conditions and associated diseases, with a specific emphasis on diets. Examining the prevalence of individuals with overweight and obesity, we observe a significant number that is crucial to address for the prevention of NCDs (12). In 2021, 54% of the adults had overweight or obesity in OECD countries on average (12). This percentage continues to rise in most countries (12).

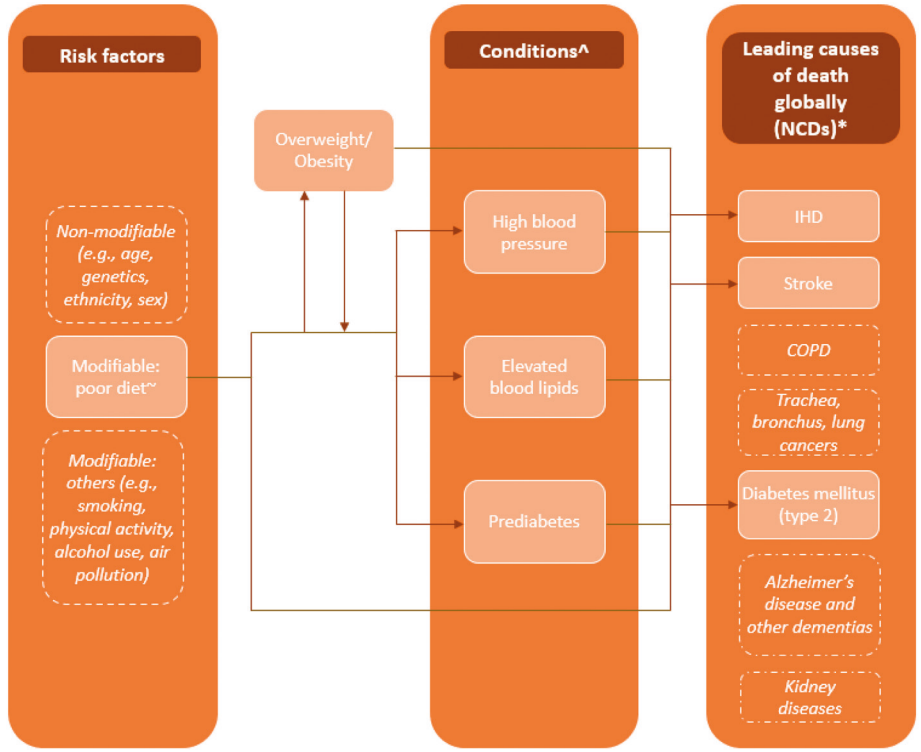


Figure 1.1: Link between different risk factors, conditions, and diseases. ˜Focusing on diets leading to overweight (no underweight). ^The conditions given in the figure are not comprehensive but meant to show that various conditions can directly or indirectly (via overweight or obesity) lead to NCDs. *NCDs that were found in the top 10 for leading causes of death globally (1). COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; NCDs, noncommunicable diseases.

(PERSONALIZED) NUTRITION

While diet plays a crucial role in preventing or managing obesity, health conditions, and diet-related diseases, a substantial number of individuals maintain unhealthy diets (12). In 2019, only an average of 15% of adults in OECD countries consumed five or more portions of fruits and vegetables daily (12). On a larger scale, unhealthy diets can eventually be deadly. Diets low in fruit, vegetables and legumes contributed to an estimated 2.7 million global deaths, leading the World Health Organization (WHO) to recommend a daily intake of at least 5 portions (12). Additionally, the WHO guidelines state that a healthy diet involves diets low in fat (less than 30% of total energy), sugars (less than 10% of total energy) and salt/sodium (less than 5 gram per day) (4). Meeting, for example, the recommended salt intake of less than 5 grams per day could prevent 1.7 million deaths annually (13). The WHO guidelines were translated into many national guidelines to promote healthy diets, such as the 'Schijf van Vijf' in the

Netherlands (11,14). However, many individuals do not adhere to these guidelines, resulting in dietary insufficiency associated with about 7.94 million deaths and 188 million disability-adjusted life years among those aged 25 years and older (15). Beyond the health implications, there is a significant economic burden, with dietary factors accounting for approximately 18.2 percent of the costs associated with IHD, stroke, and type 2 diabetes in the United States (US) (16). Scarborough et al. (17) reported that poor diet stands out as a behavioral risk factor with the most significant impact on the budget of the National Health Service (NHS) in the United Kingdom (UK). The associated ill health costs were approximately 5.8 billion pounds in 2006-2007 (17).

The heavy health and economic burden of poor diets highlights the need to improve diets and thereby prevent diet-related NCDs. Governments play a central role in establishing an environment in which people could easily adopt and maintain healthy diets (18). Various policies aimed to promote healthier lifestyles have been adopted by most OECD countries (11). Examples are the mandatory back-of-pack nutrition labelling and the implementation of taxation of foods high in calories (e.g., sugar-sweetened beverages). Besides, more and more countries have shown increasing interest in new electronic tools such as mobile health apps to promote various health-related behavioral changes. For example, as part of a family oriented Change4Life campaign in 2014, England developed a 'Be Food Smart' app that provides sugar, saturated fat, and salt content in packaged products by scanning the barcode. Unfortunately, despite those initiatives, the rates of overweight have been increasing, which indicates they have not sufficiently addressed diet-related health problems. The implementation of these policies at the population level and their effectiveness is not optimal (11), including the lack of changing nutrition related behavior (19,20).

To enhance effectiveness, guidelines and policies should transition from a population-based approach to a more individualized one, such as personalizing nutrition, considering the diverse individual responses to nutrition (21–27). Variability in responses is evident, among others, in the response of bodyweight to identical dietary interventions (28), physiological reactions to salt (29), and vitamin metabolism (30). This diversity can be influenced by factors like sex, ethnic origin, genetics, metabolic traits, environment, microbiome composition, and potentially other elements which might still need to be discovered (27). Numerous studies have identified associations between genetic factors and food metabolism, nutritional needs, dietary preferences, and disease outcomes in this context (23,31,32).

The personalization of nutrition is gaining increasing interest. However, there is still much to be discovered, including an agreed definition (23,33). There are many related and overlapping terms, such as precision nutrition, nutrigenomics, nutritional genomics and nutrigenetics, as well as adjacent (more developed) branches such as personalized medicine (34,35). For the purposes of this dissertation, we use the term 'personalized nutrition' and follow the definition by Ordovas et al. (23), who stated that it is 'an approach that uses information on individual characteristics to develop targeted nutritional advice, products,

or services'. Additionally, those authors described two conceptual bases for personalized nutrition: 1) biological evidence indicating diverse responses to foods/nutrients based on genotypic or phenotypic characteristics, and 2) examination of current behavior, preferences, barriers, and objectives, followed by the delivery of interventions that motivate and enable each person to make suitable changes to their eating pattern (23).

Besides difficulties in reaching consensus on the definition of personalized nutrition, there are also several challenges when it comes to translating and applying the advancements in personalized nutrition approaches to human studies. One example is the challenge of creating a personalized nutrition infrastructure (33). Some studies somehow have succeeded in addressing (some of) the challenges associated with personalized nutrition interventions and examining the effectiveness of such interventions (36). However, those interventions have not yielded consistent findings (36,37). For example, the Food4Me study showed positive dietary behavior changes in the personalized nutrition group compared to the non-personalized control group (38). However, the incorporation of phenotypic (e.g., glucose and total cholesterol) or genotypic data, along with the analysis of current eating patterns, did not enhance intervention effectiveness (38). Moreover, a study by Frankwich et al. (39) showed no significant differences in lipid profile among participants who received genotype-based diet and standard therapy. In contrast, Rein et al. (40) showed the benefits in glycemic measures in newly diagnosed type 2 diabetes patients of including personal information in dietary recommendations (i.e., personalized diet). The personalized diet in this study utilized a machine learning algorithm that integrated clinical (e.g., blood tests and anthropometrics) and microbiome features to predict individual postprandial glucose responses. This was compared to the commonly recommended Mediterranean-style diet (40).

Given the existing uncertainties about the effectiveness of personalized nutrition, questions can be raised about whether it is a potential solution (hope) or just a hype in addressing diet-related diseases. To move forward, developers, policymakers and other stakeholders should address existing challenges and explore its effectiveness simultaneously.

PREVENTOMICS

One project that tackled various challenges in the field of personalized nutrition is PREVENTOMICS (41). Financed through the European Horizon 2020 initiative, this recently completed project investigated the potential of advanced technologies for personalized nutrition across individuals with normal weight, overweight, and obesity. Specifically, it investigated the use of omics, with a specific focus on metabolomics, as a key input for personalized nutrition advice (8). The project not only harnessed existing omics technologies but also introduced innovations in metabolomics, facilitating an unprecedented level of precision in characterizing individual metabolism.

The initial steps in developing personalized nutrition advice within the PREVENTOMICS project are illustrated in Figure 1.2A. The figure demonstrates the utilization of metabolomics, proteomics, and genetics (35 single nucleotide polymorphisms) data to categorize individuals into five distinct metabolic clusters, representing the core health processes (8). Easily accessible samples such as plasma, serum, urine, and saliva were used to retrieve this data. The health processes represent relatively independent clusters of various metabolites and protein biomarkers. For each of the five core health processes (carbohydrate metabolism, lipid metabolism, inflammation, microbiota, and oxidative stress), the project generated a metabolic score. This score indicated the deviation from the average, with higher scores signaling a greater deviation. Dietary advice for health improvement was then tailored based on deviations in an unhealthy direction (8).

What sets PREVENTOMICS apart from other personalized nutrition initiatives is not only its advances in omics but also its practical integration of these technologies. The project developed a user-friendly and comprehensive platform referred to as the Decision Support System (DSS) (see Figure 1.2B) (8). This innovative platform integrated phenotypic characterization at the metabolomic level with individual's genotype, lifestyle, health status, preferences, and physiological status.

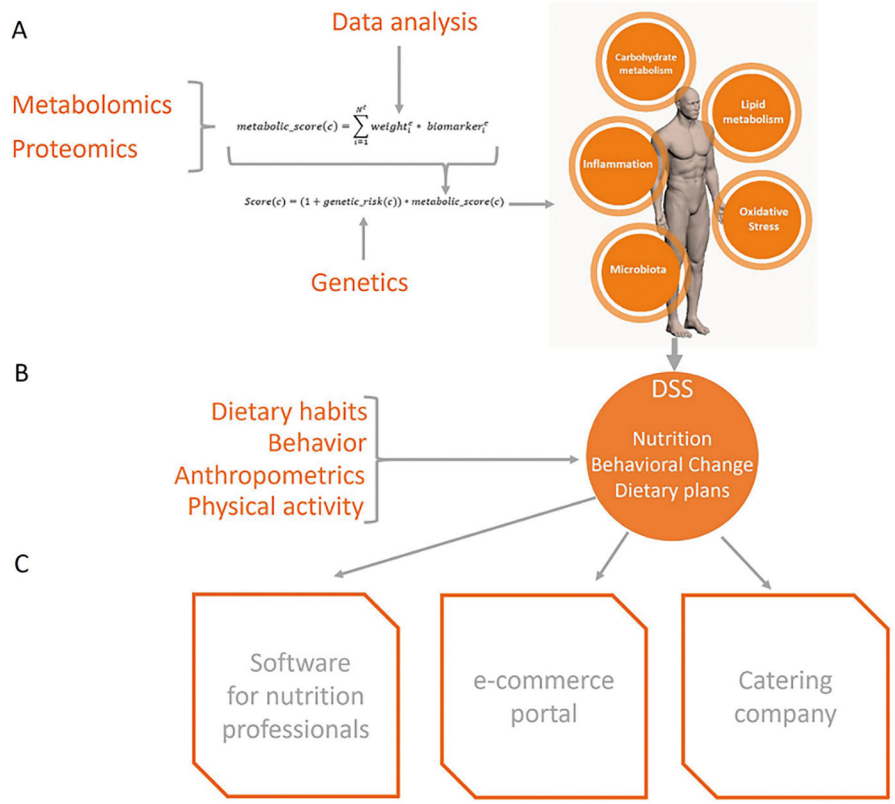


Figure 1.2: Implementation of the proposed personalized nutrition approach in the PREVENTOMICS project, as presented in a study by Keijer et al. 2023 (8): A) The system integrated metabolomic, proteomic, and genetic data along with the results of data analysis to score the five core health processes. B) The scores for core health processes were then combined with behavioral information within a decision support system (DSS). C) The decision support system was accessed by various software programs capable of retrieving specific information about the user to formulate personalized recommendations.

Furthermore, the platform was integrated into three distinct use cases (see Figure 1.2C), resulting in three PREVENTOMICS interventions (8,42): [1] Software for nutrition professionals: integration of the platform with software to support healthcare professionals in formulating personalized dietary plans for consumers, [2] E-commerce portal: integration of the platform at the retailer level for personalized recommendations during shopping, and [3] Catering company: integration of the platform to develop and deliver easy-to-prepare personalized meal boxes. These three PREVENTOMICS interventions were studied in four different trials conducted in Poland, the United Kingdom (UK), Spain and Denmark. Detailed discussions of these interventions will follow in subsequent chapters, with a summary provided below.

Software for nutrition professionals

In this study, the platform was incorporated into nutrition professionals' software (MetaDieta) and implemented in two countries, Poland, and the UK. In both countries, comparable study protocols were employed, involving a 4-month trial focusing on participants aged 18 to 65 years with abdominal obesity and a BMI between 25 and 40 kg/m^2 (43,44). Participants were assigned to three groups: 1) personalized plan + behavioral change (PP+B); 2) personalized plan (PP), and 3) control. Participants in the control group received general dietary recommendations by the dietitian, while the PP+B and PP groups received personalized advice by the dietitian based on the factors described in Figure 1.2A-B. The MetaDieta software processed recommendations from the platform for dietitians to create individualized dietary plans using various factors. Additionally, participants used the MetaDieta app for dietary support, intake monitoring, and dietitian contact. The PP+B group received additional behavioral prompts via the MetaDieta app. Consultations with the dietitian were scheduled once a month.

E-commerce portal

In this PREVENTOMICS intervention, the platform was incorporated into an E-commerce portal, also referred to as the ALDI supermarket microsite, with the intervention implemented in Spain. The study was a 4-month single-blind randomized placebo-controlled trial, in which healthy adults (18-65 years) were randomly assigned to three groups (45): 1) control, receiving general recommendations based on the Mediterranean diet; 2) personalized nutrition (PN), receiving personalized recommendations adapted to metabolomics, proteomics, genetics, and other factors (see Figure 1.2B); 3) personalized plan (PP), including PN and a behavioral change program. Recommendations were delivered through a specially developed ALDI microsite. This microsite accessed the recommendations from the platform through API-based calls, matching them to food products in ALDI's catalogue (personalized for PN and PP or general for control), considering context attributes like season, weather, and location (8,42,45). This process provided participants with a categorized list of recommended products.

Catering company

In this study, the platform was incorporated into a catering company software (i.e., Simple Feast), with the intervention implemented and tested in Denmark (46,47). It included a 10-week randomized, single-center, parallel-group, double-blinded trial, targeting overweight and obese adults, with two arms: Personalized Plan (PP) and control. Participants were allocated in a 1:1 ratio, stratified by the five clusters. Both groups received easy-to-prepare plant-based meals in boxes twice a week (12 meals/week) from Simple Feast (Copenhagen, Denmark), with isocaloric and guideline-compliant meals. The meals in the PP group were based on a cluster-specific list and included some bioactive compounds especially beneficial for the metabolic function of individuals corresponding cluster. Additionally, this group received a behavioral program through Onmi's app with active "Do's" tailored to their cluster. The control group also received a behavioral program, but with general informational messages. Both groups received 2-3 electronic push notifications per week (46,47).

COST-EFFECTIVENESS ANALYSES

While the effectiveness of these PREVENTOMICS interventions is still uncertain, they hold the potential to improve health outcomes (47). However, the innovative approach of the PREVENTOMICS interventions introduces additional expenses, primarily due to the high costs associated with omics analyses (48). With the constraints of limited resources in national health systems, it becomes crucial that personalized nutrition interventions are not only effective but also cost-effective, ensuring optimal utilization of scarce resources to achieve maximum health benefits (49).

Economic evaluations (i.e., cost-effectiveness analyses) help shed light on whether interventions, such as the PREVENTOMICS ones, are cost-effective and thereby assist healthcare decision-making for different stakeholders (49,50). In short, economic evaluations involve the comparison of costs and effects among alternative strategies. There are different variants of these economic evaluations; all using monetary units to measure costs but varying in their measurement of effectiveness. Although "cost-effectiveness analysis" is commonly used as a general umbrella term, it also denotes a specific type of economic evaluation. In that specific type of cost-effectiveness analysis (CEA), the effectiveness measure is expressed in natural units, such as life years gained or points of blood pressure reduction. In a cost-benefit analysis (CBA), effectiveness is denoted in monetary units, while a cost-minimization analysis (CMA) assumes equal effectiveness for both alternatives. Lastly, in a cost-utility analysis (CUA), the effectiveness measure is expressed in quality-adjusted life years (QALYs), representing healthy years (49).

The last mentioned CUA is often used in practice as it is useful for comparing interventions in different areas of healthcare (49). It employs an incremental cost-utility ratio (ICUR) as a conclusive measure of cost-effectiveness, providing decision-makers with a focused outcome. Essentially, this ratio divides the additional costs of one intervention over the other by the additional effects it delivers (Δ costs / Δ QALYs = ICUR). Typically, this ICUR is compared to a specific willingness to pay (WTP) threshold, which varies by country. A positive ICUR, where both incremental costs and effects are positive and fall below the WTP threshold, suggests the intervention could be considered cost-effective. A negative ICUR, where incremental costs are negative and incremental effects are positive, also deems the intervention cost-effective (49).

As previously mentioned, this outcome holds relevance for various stakeholders in healthcare decision-making. Given that the PREVENTOMICS interventions are in a pre-market phase and open to further development, the CEAs conducted in this dissertation can be regarded as early CEAs. 'Early' is defined by Love-Koh (51) as 'being any point before healthcare payers are making decisions about whether or not to adopt the intervention'. The resulting ICURs and related conclusions from an early CEA are particularly pertinent for developers and policymakers, informing aspects like development (e.g., design), market access, and pricing (50,52–54). Utilizing economic models for these investigations is crucial as there is often little

or no data available in this phase (51). Ultimately, this process aids in the 'stop or go' decision by determining whether the PREVENTOMICS interventions are considered cost-effective in this phase.

PREFERENCES

While the cost-effectiveness of interventions is a crucial factor for decision-making, there is a growing recognition of the importance of patient preference data in healthcare decision-making (55–57). The National Institute for Health and Care Excellence (NICE) in the UK, for example, acknowledges the role of patient preference studies as valuable evidence alongside other types of data (58). The US Food and Drug Administration (FDA) defines patient preference information as 'qualitative or quantitative assessments of the relative desirability or acceptability to patients of features that differ among alternative health states, health interventions, or services' (59). Other agencies that evaluate health technologies (i.e., health technology assessment (HTA) agencies) have also expressed interest in incorporating patient preferences into decision-making (60).

Integrating patient preferences into the assessment of a health technology (i.e., HTA) is justified for several reasons: it upholds patients' right to participate in decisions affecting them, enhances decision-making by leveraging patients' experiential knowledge, and contributes to the social legitimacy of decisions (55). Employing a structured process to unveil preferences can involve using both qualitative and quantitative preference measurement methods (61). However, some argue in favor of quantifying patient preferences to ensure their proper consideration in healthcare decision-making (62).

A commonly used quantitative method for eliciting preferences is a discrete choice experiment (DCE) (61). This method is widely employed in healthcare and food research (61,63). In a DCE, respondents are asked to state their preference repeatedly by trading-off alternatives (i.e., hypothetical interventions) through a series of questions (i.e., choice tasks) (64,65). These alternatives have various characteristics (attributes) of which levels vary between alternatives and choice tasks. With statistical methods, the relative importance of attributes and levels could be analyzed, aligning with random utility theory, where the chosen alternative offers the highest utility to the respondent (66–69). These methods can also determine marginal rates of substitution, such as the WTP (66). This reflects the amount users would be willing to pay to obtain additional benefits such as improved health. Given that users of (personalized) nutrition interventions, in particularly PREVENTOMICS interventions, may bear part of the intervention costs, estimating WTP is crucial in the nutrition field (68,70).

HEALTH TECHNOLOGY ASSESSMENT (HTA)

When assessing personalized nutrition interventions to guide healthcare decision-making, it is crucial to acknowledge that various considerations exist beyond mere cost-effectiveness,

preferences, and WTP. Broadening the scope of assessments through HTA is essential for a comprehensive evaluation of interventions' overall value (71,72). The term 'value' encompasses dimensions such as clinical effectiveness, safety, costs, and ethical and legal considerations of a health technology (72). To determine this value, an HTA applies a multidisciplinary process and uses explicit methods which could be applied at different points in the lifecycle of a health technology (72).

An 'early' HTA, defined by IJzerman et al. (54) as 'all methods used to inform industry and other stakeholders about the *potential value* of new medical products in *development*, including methods to quantify and manage uncertainty', could help in promoting transparency and government accountability. Additionally, it could aid technology developers in understanding how their technologies will be assessed. This early HTA could reduce the time and financing required for a product to gain market entry or get reimbursed (54,73,74).

Previous HTAs have often focused solely on costs, health effects, and cost-effectiveness of nutrition interventions, neglecting broader societal and healthcare issues (75). To address variations in the extent and scope of HTA and discrepancies in reporting results, the European Network for Health Technology Assessment (EUnetHTA) developed the HTA Core Model (76). Figure 1.3 illustrates the domains covered by this model, offering either a comprehensive (broad scope) or rapid (limited scope) assessment.

Conducting an early HTA using the HTA Core Model provides advantages such as (timely) identifying key assessment components, offering a structured analysis of (early) scientific evidence, and highlighting existing gaps, informing subsequent decision-making steps (52,54,77,78). Ultimately, it offers insights into whether personalized nutrition is a mere hype or a hopeful avenue.

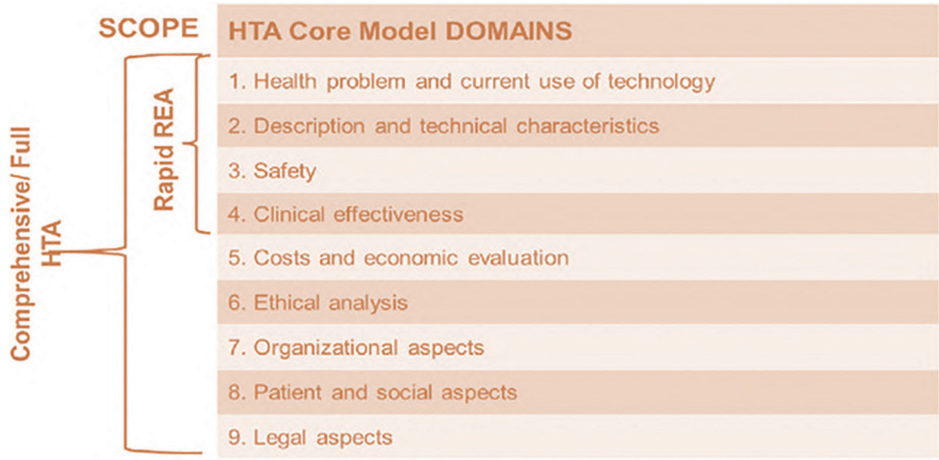


Figure 1.3: Different domains in an HTA as published by Kristensen et al. (78).

THESIS AIM

This PhD thesis investigated the potential of personalized nutrition interventions, using the PREVENTOMICS interventions as examples, by conducting an early HTA. The overarching goal was to provide insights that would assist diverse stakeholders in healthcare decision-making, guiding the development and implementation of personalized nutrition interventions into the market to mitigate diet-related diseases. To achieve comprehensive conclusions, the following key research questions were addressed:

- What is the potential cost-effectiveness of personalized nutrition interventions, including the PREVENTOMICS interventions studied in different countries?
- What are the preferences and willingness to pay of the general population regarding personalized nutrition interventions?
- Beyond cost-effectiveness and preferences, what other crucial HTA aspects should be considered for the development and implementation of personalized nutrition interventions?
- Can personalized nutrition interventions genuinely be regarded as a 'hope,' or is it merely a 'hype'?

OUTLINE

To address the research questions, the thesis is structured into seven chapters, which are organized into three distinct parts. This structure, along with the titles assigned to each part, is inspired by another crucial modifiable risk factor for NCDs: physical activity or sports.

While this thesis did not thoroughly explore this risk factor, the structure of the thesis was chosen in recognition of its importance in preventing NCDs. Moreover, the absence of sports or other physical activity would render the completion of this thesis incomplete, as detailed in the preface. Therefore, Matveyev's Model was chosen, named after the Soviet sports scientist and coach Leo Matveyev, as the foundational concept (79–81). In short, Matveyev's model is fundamental in the periodization of sports training. Periodization refers to the systematic planning and organization of training over specific periods (cycles) to optimize athletic performance during competition. In other words, it involves a logical and phased approach to manipulate fitness and recovery cycles. The goal is to enhance the likelihood of achieving specific performance objectives while minimizing the risk of nonfunctional overreaching, overtraining, and injuries (81). The phases in this model align with the outline presented below and is visually presented in Figure 1.4.

Part I – Preparation: establishing a foundation for cost-effectiveness analyses

The preparatory phase in sport is crucial for maximizing performance during the competition phase (80). In other words, this initial stage establishes the physiological foundation for performance. This encompasses both general and specific preparation, involving shifts from extensive to intensive methods and technique training (81,82). Translating this to the thesis outline, Part I serves as the foundation for the analyses (competitions) that were done in Part II. General and specific preparations correspond to **Chapter 2** and **3**, respectively. **Chapter 2** entails a general preparation through a systematic review. The review assessed the current landscape of cost-effectiveness studies on personalized nutrition interventions. This established the foundation for decisions regarding the development and utilization of a cost-effectiveness model to examine the lifetime cost-effectiveness of personalized nutrition interventions. The cost-effectiveness model used in the analyses found in Part II is described in detail in **Chapter 3.** Moreover, in this chapter, the potential impact of prevention was assessed, with a focus on the health and economic burden of obesity. With this more specific preparation, the stage was set for the subsequent chapters in Part II.

Part II – Competitions: conducting cost-effectiveness analyses

The competition phase is the period in which athletes aim to maximize their performance, marked by competitions that include pre-competitive and main competition stages (80,81). Building on the foundation established in Part I, Part II of this thesis investigated the cost-effectiveness of personalized nutrition interventions developed during the PREVENTOMICS project. Using the language of 'sport competitions', it scrutinizes interventions to determine which intervention (within or across the chapters) 'wins' from the other in terms of cost-effectiveness. **Chapter 4** presents the results of a cost-effectiveness analysis for the clinical trial conducted in Denmark, which examined the cost-effectiveness of personalized nutrition plans versus general nutrition plans for adults with overweight and obesity. In **Chapter 5**, the focus shifts to adults with overweight and obesity in the UK and Poland, evaluating the cost-effectiveness of personalized nutrition plans with or without a behavioral change program compared to a control group. In **Chapter 6** the cost-effectiveness of a personalized nutrition plan, with or without a behavioral change program, versus a control group in healthy, overweight, and obese adults in Spain was assessed. All cost-effectiveness studies utilized the model explained in **Chapter 3**. The model was adjusted to the country in which the trial took place to estimate the lifetime cost-effectiveness of personalized nutrition interventions using trial data.

Part III – Transition: to a broader health technology assessment perspective

After the demanding competition phase, athletes enter a transition phase before entering a new annual training plan, which starts again with the preparation phase (i.e., next cycle) (80). This transition phase allows the athlete to actively relax and to recover from physical and psychological stress (79,80). Additionally, it enables a critical assessment of various aspects, including goals, mental factors, and performance standards (80). This comprehensive evaluation is essential to adequately prepare athletes both mentally and physically for the upcoming cycle.

In the context of this thesis, we shift the focus from cost-effectiveness analyses in Part I and Part II to a more comprehensive HTA perspective, primarily emphasizing the broader meaning of the transition phase. **Chapter 7** examined a facet that is of growing importance in healthcare decision-making: preferences. Through DCEs in Europe and the US, it explores preferences and willingness to pay for personalized nutrition interventions in the general population. In **Chapter 8**, the perspective broadens further to a more holistic HTA perspective, leveraging the EUnetHTA HTA core Model.

The thesis concludes with a (general) discussion (**Chapter 9**) covering all chapters. While each chapter contains discussions specific to their research focus, this final section examined overarching and additional discussion points. It evaluates the strengths and limitations of the thesis work, including a broader assessment of personalized nutrition intervention. The chapter offers recommendations and implications for diverse stakeholders. Applying Matveyev's model, these insights can inform decisions about the 'next cycle' of development, implementation and/or research.

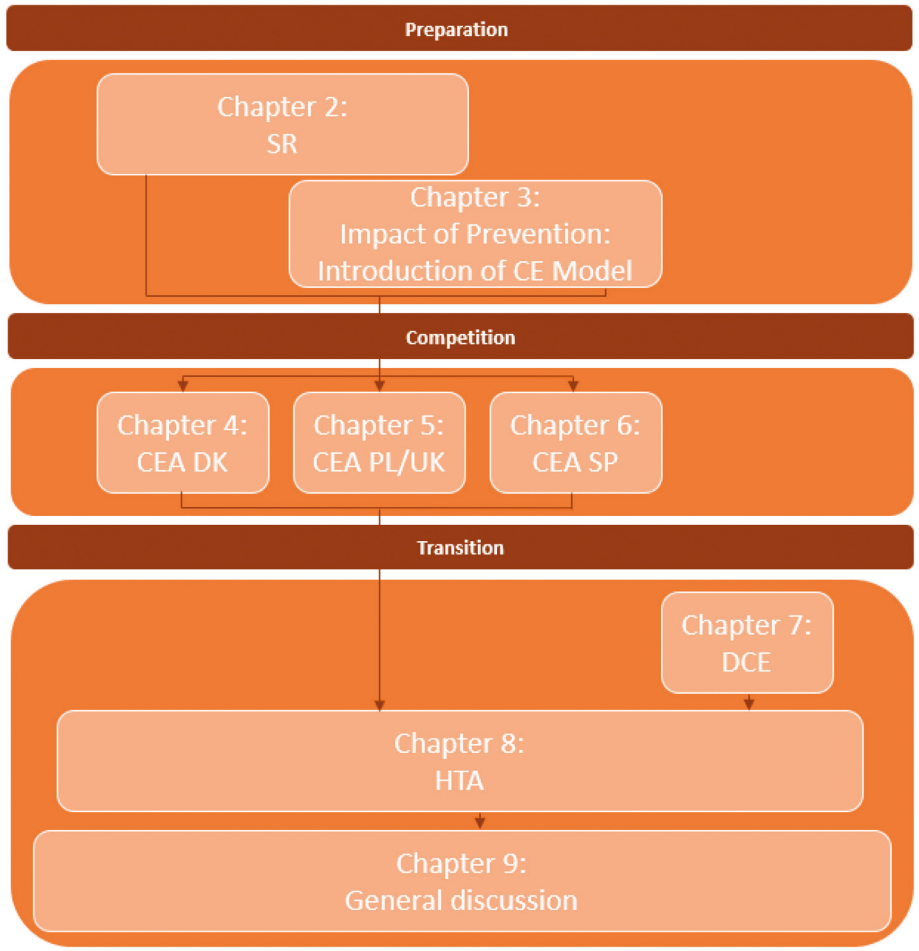


Figure 1.4: Outline of this thesis. CE, cost-effectiveness; CEA, cost-effectiveness analyses; DCE, discrete choice experiment; DK, Denmark; HTA, health technology assessment; PL, Poland; SP, Spain; SR, systematic review; UK, United Kingdom.

Part 1

Preparation: establishing a foundation for cost-effectiveness analyses

Chapter 2

A systematic review of cost-effectiveness studies of interventions with a personalized nutrition component in adults

Milanne M.J. Galekop, Carin A. Uyl-de Groot, W. Ken Redekop

Value in Health 2021; 24 (3): 325-335.

ABSTRACT

Objectives

Important links between dietary patterns and diseases have been widely applied to establish nutrition interventions. However, knowledge about between-person heterogeneity regarding the benefits of nutrition intervention can be used to personalize the intervention and thereby improve health outcomes and efficiency. We performed a systematic review of cost-effectiveness analyses (CEAs) of interventions with a personalized nutrition (PN) component to assess their methodology and findings.

Methods

A systematic search (March 2019) was performed in 5 databases: EMBASE, Medline Ovid, Web of Science, Cochrane CENTRAL and Google Scholar. CEAs involving interventions in adults with a PN component were included; CEAs focusing on clinical nutrition or undernutrition were excluded. The CHEERS checklist was used to assess the quality of CEAs.

Results

We identified 49 eligible studies among 1792 unique records. Substantial variation in methodology was found. Most studies (91%) focused only on psychological concepts of PN such as behavior and preferences. Thirty-six CEAs were trial-based, 13 were modeling studies and 4 studies were both trial- and model-based. Thirty-two studies used quality-adjusted life year as an outcome measure. Different time horizons, comparators and modeling assumptions were applied, leading to differences in costs/ quality-adjusted life years. Twenty-seven CEAs (47%) concluded that the intervention was cost-effective and 75% of the incremental cost-utility ratios were cost-effective given a willingness to pay threshold of $50,000 per quality-adjusted life year.

Conclusions

Interventions with PN components are often evaluated using various types of models. However, most PN interventions have been considered cost-effective. More studies should examine the cost-effectiveness of PN interventions that combine psychological and biological concepts of personalization.

INTRODUCTION

There are well-established links between poor dietary patterns, representing a complex set of highly correlated dietary exposures (83) and an increased risk of different diseases (23,84). Obesity may be an intermediate outcome of these links (85), since obesity often leads to diet-related diseases such as type 2 diabetes, heart disease, stroke, and cancer (23). In other cases, poor dietary patterns can arise from other problems (e.g., hip fracture) which may lead to malnutrition and possibly result in disorders such as functional disability and impaired cognitive function (86). In this regard, diet-based prevention of obesity and malnutrition can help to reduce the frequency of various diseases, improve health outcomes, and reduce economic burden (87). This knowledge has led to the development of many nutrition interventions based on population averages. However, although these nutrition interventions might have an acceptable average overall effectiveness (i.e., population level), they often have poor individual-level effectiveness (48,84). Studies have shown this might be caused by inter-individual variability of metabolic responses to specific diets and food components that affect health (37,88). Knowledge about an individual's response could lead to a personalized intervention to maximize the potential health benefits of these diets and food components (88).

Various personalized nutrition (PN) interventions, which can be defined as an approach that uses information on individual characteristics to develop targeted nutritional advice, products, or services (23), have been developed and assessed. For example, the Food4Me study found that internet-delivered personalized advice produced larger and more appropriate changes in dietary behavior than a conventional (one-size-fits-all) approach (38). However, policy decisions must be guided by their ability to improve health outcomes and their cost-effectiveness (89), given the ever-present tension between effectiveness and financial constraints (90). In fact, various cost-effectiveness analyses (CEAs) of nutrition interventions have been published, and systematic reviews of these CEAs have been conducted (89,91,92). However, these reviews often focused on specific diseases or interventions (e.g., salt reduction (92)). To our knowledge, no review has ever focused specifically on PN. Therefore, we reviewed and critically appraised CEAs of personalized interventions with a nutrition component in adults by describing and assessing their methodology, findings, and quality. This can support policy decisions around PN (23,90). In addition, this review can help to design and improve future CEAs of PN interventions.

METHODS

Literature Search

The approach in this review was based on a series of 3 articles describing methodological guidelines for systematic reviews of CEAs (90,93,94). The term CEA was used as an overarching term for full economic evaluations such as CEA and cost-utility analysis (CUA). A biomedical information specialist helped to design the systematic search strategy; the search was

performed on March 8, 2019. Five bibliographic databases were used (i.e., Embase, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google Scholar). Search terms (including MESH terms and text words) were terms related to CEA (e.g., economic evaluation), nutrition (e.g., diet therapy), and personalization (e.g., individual). Specific search queries are provided in Appendix 2.1.

Inclusion criteria were full texts, English-language publications of CEAs involving interventions with a PN component focusing on adults. Interventions involving children, clinical nutrition, and studies of adults with underweight (body mass index <18.5) were excluded. Appendix 2.2 provides detailed information about inclusion/exclusion criteria.

Two authors (MMJG, WKR) independently reviewed titles and abstracts of all articles (including CEAs found via screening systematic reviews) to determine which ones met the eligibility criteria. Interrater agreement about the eligibility for full-text review was then assessed and found to be moderate (Cohen's kappa: 0.498) (95,96). Any disagreement not resolved by discussion resulted in full-text screening. Full-text versions of the articles were then examined to determine which ones met all eligibility criteria. This was done primarily by the first author (MMJG) using a detailed list of criteria, and any doubt was discussed with a second reviewer (WKR).

Data Extraction/Analyses

Data extraction was initially done by one author (MMJG) and checked by a second author (WKR). General features of the studies that might influence economic outcomes (e.g., intervention characteristics including definitions) were collected as well as economic findings themselves (e.g., incremental cost-effectiveness ratio and incremental cost-utility ratio (ICUR)). Summary tables and figures of these characteristics were created, and each intervention was matched to a PN concept. Previous literature defined the conceptual basis for PN; specifically, personalization can be based on the analysis of current eating habits, behavior, preferences, barriers, and objectives ("psychological concept") or on the biological evidence of differential responses to foods/nutrients (i.e., biomarkers, genotype, and microbiota) ("biological concept") (23,97).

Conclusions of the authors regarding the cost-effectiveness of the intervention were collected and arranged into 4 categories: "yes" (cost-effective), "no" (not cost-effective), "sometimes" (only cost-effective in some subgroups), and "no conclusion." Total costs and ICURs were inflated to 2019 costs using the country-specific Consumer Price Index (98) and converted to Unites States dollars (US$) using the purchasing power parity (99). If the cost year of the study was not specified, it was assumed to be the year of publication. To determine whether an intervention would be considered cost-effective, ICURs were compared with 2 willingness to pay (WTP) thresholds (values in US$ per quality-adjusted life years (QALY)): $20,000 (close to the thresholds of £20,000 ($25,937 (100)) used in United Kingdom and €20,000 ($23,680 (100)) in the Netherlands for interventions targeting diseases with a low disease

burden (101)) and $50,000 (widely used in the United States). The incremental net monetary benefit (iNMB) was calculated by valuing incremental QALYs in monetary values using both thresholds. Furthermore, we examined possible relationships between the results (QALYs and costs) and general features (i.e., population, intervention, choice of comparator) and modeling choices (i.e., time horizon, perspective, discount rate, number of health states, intermediate outcomes, and assumptions regarding intervention effects).

Quality Assessment

The quality of all studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (102), which is preferred when modeling studies are included (94). This checklist consists of 24 items, subdivided into six categories: [1] title and abstract; [2] introduction; [3] methods; [4] results; [5] discussion; and [6] other. There are 3 possible answers for each item: fulfilled, not fulfilled, and not applicable.

RESULTS

The database searches identified 2864 articles (Figure 2.1 (103)); an additional 15 records (104–118) were identified manually via systematic reviews (119–124). After removing duplicates, 1792 records were screened on title/abstract, and 1577 records were excluded based on the eligibility criteria. The remaining 215 articles underwent full-text screening, which resulted in a final list of 49 articles. Most studies were performed in Europe (44% (n=24) (106,108,109,111,117–119,125–141)), of which 10 studies were in the United Kingdom (106,108 ,119,125,130,134,136,137,139,140). Almost as many were performed in North America (n=22 (42%) (104,107,112–114,116,142–157)). Dalziel et al. (158) conducted different CEAs, of which we included 5 (127,137,150,159,160) which led to a total of 53 unique CEAs (48+5=53). Since several characteristics of interventions differed between study arms, some frequencies of characteristics were reported per arm.

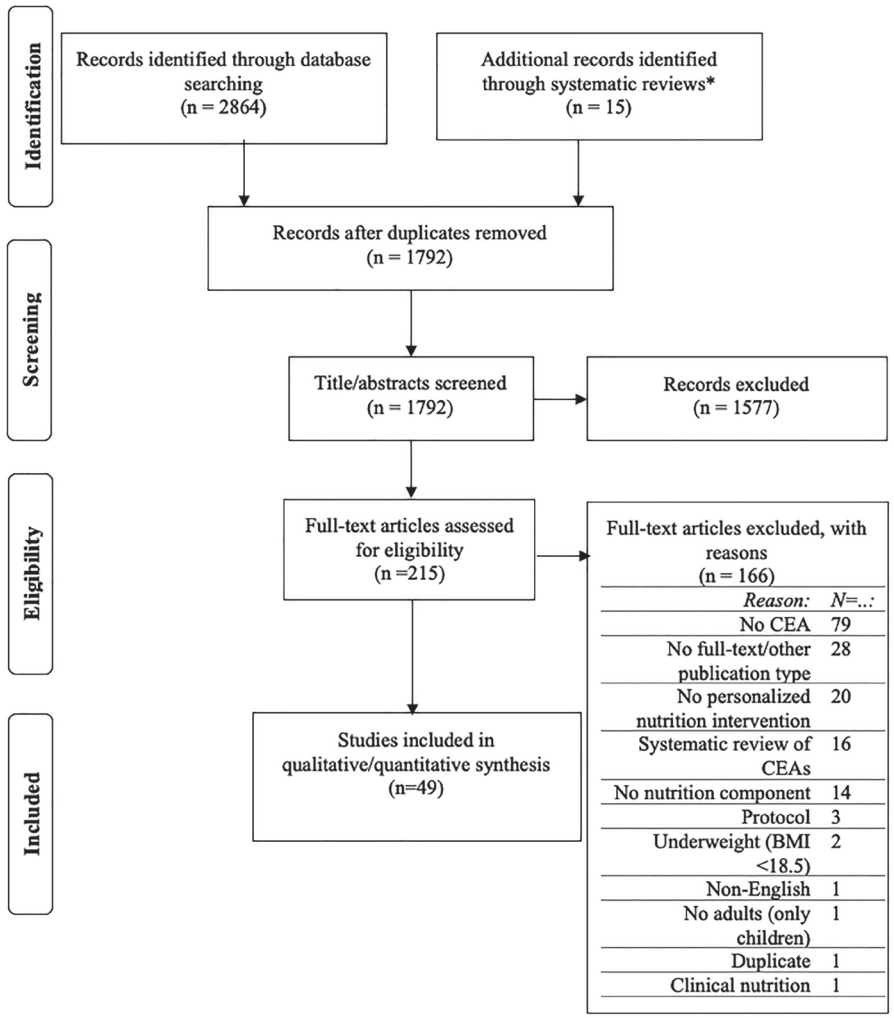


Figure 2.1: PRISMA diagram. CEA, Cost-effectiveness analysis; n, number of records. *These systematic reviews were found in the database searches and studies in these systematic reviews were screened for relevant articles. All relevant articles were then included in the title/abstract screening process.

Population and Intervention

Figure 2.2 provides an overview of the general study characteristics (i.e., populations, interventions, methods); Appendix 2.3 provides detailed information per study. Nine studies focused on interventions related to the Diabetes Prevention Program (DPP) (104,112–116,123,131,153) and 4 on the Diabetes Prevention Study (DPS) (109,117–119,158). The DPP trial determined whether lifestyle intervention or pharmacological therapy (metformin, placebo)

prevented or delayed the development of type 2 diabetes in the United States (161). DPS was a Finnish randomized controlled trial with a personalized lifestyle intervention arm (162,163).

Fifteen CEAs (105–107,110,111,125,142,144–146,151,155,157,158) focused on the obesity/diabetes/impaired glucose tolerance population but studied interventions other than DPP/DPS (Figure 2.2, Appendix 2.3). These interventions were mostly computer-based (n=6 studies;7 arms (106,107,110,145,155,157)) and comprised interventions with only a nutrition component (105,110,125,144,145,159) instead of exercise and nutrition as in DPP/DPS. Other CEAs focused on general/healthy populations (n=6 (117,135,149,154,158)) or "other" populations such as depression (n=14 (126,128–130,134,136,138–140,143,147,152,156,164)). The only CEA in the review that assessed an intervention based on only the biological concept of PN was found here (128). CEAs found in malnourished (at risk of undernutrition) populations (n=5 (132,133,141,165,166)) studied interventions that were similar to the interventions studied in CEAs of other populations. For example, individual counseling was studied in both CEAs of malnourished populations (141,165) as well as CEAs of other populations (144,160).

In total, 34 studies had 1 or more arms that defined PN as "individualized" nutrition (arms: 46%, n=45), followed by 18 studies (109,112–114,119,123,127–129,131,135,137,139,141,143,154,157,162) that used "tailored" (arms: 23%, n=23) and 18 studies (106,125,126,129,130,133–137,139,143,149,150,154,155,159,164) that used "personalized" (arms: 19%, n=20) (Figure 2.2, Appendix 2.3). Ordovas et al. (23) found that personalized nutrition partly overlaps with different terms such as individualized and tailored, but they have slightly different meanings; tailored interventions group individuals with shared characteristics, whereas personalized and individually tailored mean similar things and involve delivery of interventions suited to a particular individual. Most studies (n=48) included arms (n=60) that were based on the psychological concept of PN. One study (128) (n=3 arms) applied personalization based on the biological concept, and 4 studies (140,144,150,166) (n=4 arms; 1 arm per study) used interventions that comprised both concepts (integrated approach).

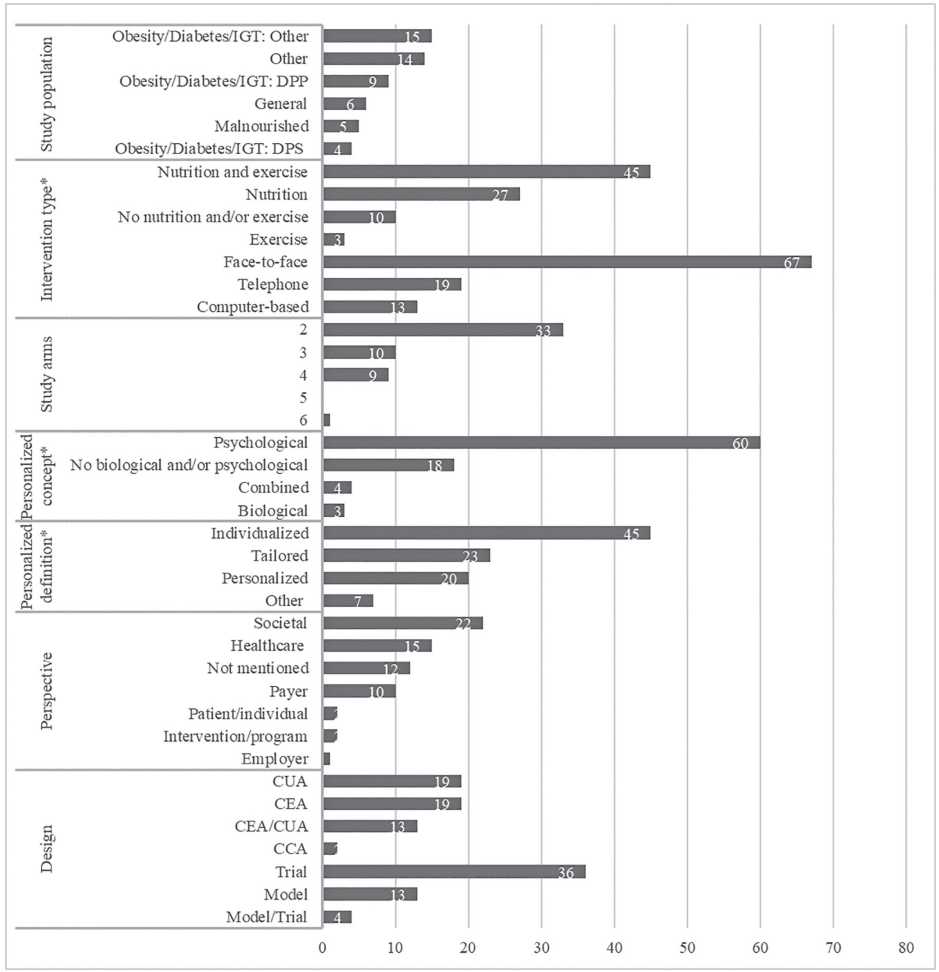


Figure 2.2: Frequencies regarding study design elements. CBA, cost-benefit analysis; CCA, cost-consequences analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; IGT, Impaired glucose tolerance. Study design elements are shown on the y-axis and frequencies are shown on the x-axis. Frequency reflects the number of studies or study arms (*). (+): Frequency was based on intervention arms only (no comparator arms). (^): Frequency exceeded total number of studies (53) or arms (138) since some studies included several element types in their analysis.

Methodology of the CEAs

Nineteen studies (105,106,112,114,116,118,119,125,128–130,136,138–140,153,156,164,165) involved a CUA and reported QALYs as outcome measure; 13 studies (104,109,117,126,127, 133,135,137,141,147,150,159,166) conducted both a CEA and CUA. Other studies conducted a CEA (n=19 (107,110,111,113,115,123,131,134,142–146,149,152,154,155,157,160)) and cost-consequence analysis (CCA) (n=2 (132,151)); these studies used other outcome measures such as weight change (n=10 (107,127,132,133,141,142,146,159,160,167)) and life years gained (n=6

(109–111,113,117,123)) (Figure 2.2, Appendix 2.3). Two CUAs also calculated the iNMB using WTP thresholds not specifically related to nutrition interventions (135,156). Most studies (n=36) were trial-based, 13 were model-based (109,110,112–114,116–119,123,128,131,153) and 4 studies used both (127,137,150,159). The range of time horizons among the trial-based studies was 0.08 years (4 weeks) (134) to 6 years (127,129), whereas the range of time horizons in the model-based studies was 3 years (131) to lifetime (109,112,116,117,123,128). See Appendix 2.4 for frequencies of time horizons.

The societal perspective was most commonly used (n=22 (104,106,109,114,116–118,127,130,131,133,135,137,139,141,147,150,153,156,159,160,164)), followed by healthcare (n=15 (104,115,116,125,126,129,130,136,138,144,145,153,164–166)) and payer (n=10 (112–114,117,119,123,128,131,155,157)); other CEAs used a patient perspective (n=2 (114,142)), intervention/program (n=2 (142,143)), and employer (n=1 (147)) (Figure 2.2, Appendix 2.3). Most studies used “usual care” or “standard care” as comparator. However, some studies used other comparators; Herman et al. (116) used metformin, and Sukhanova et al. (154) used a comparator (untailored program) that was similar to the intervention (tailored program) but did not have a personalized component.

CUAs of DPP/DPS interventions evaluated almost homogeneous populations, interventions, comparators, and outcomes (PICOs) (Figure 2.2, Appendix 2.3). However, in some CUAs subgroup analyses were done (e.g., overweight, borderline, and obese) (109) and variation in comparators was observed; drug comparators (104,116), general lifestyle recommendations or no intervention were used (109,112,114,118,119,153,158). Moreover, variation was found in the CUA models (i.e., different assumptions and approaches). First, time horizons varying from 3 years (104) to lifetime (109,112,116) and societal (104,109,114,116,118,153,158), payer (112,119), and health system (104,116,153) perspectives were used. Second, CUAs of the DPS intervention were done with Markov models using 3 (119), 4 (109,158) or 7 (118) health states. Additionally, different assumptions were made about the treatment effect over time and intermediate outcomes; the intervention effect was modeled using cardiovascular disease (CVD) risk factors and body mass index (109) through CVD risk factors alone (118), or no CVD risk factors were modeled (119). Third, models in DPP interventions varied; 4 (112,153) or 5 (116) health states were used in Markov models and Eddy et al. (114) used the Archimedes model (addresses what happens underneath clinical states, between annual jumps and inside transition probabilities). See Appendices 2.3 and 2.5 for detailed information about modeling approaches in DPP/DPS studies.

Table 2.1: Additional analyses of incremental net monetary benefits.

	Lowest Value in $ (WTP $50,000)	*Highest Value in $ (WTP $50,000)*	*Mean in $ (WTP $50,000)*	*Number of iNMB values*
iNMB categorized by population				
Obesity/diabetes/IGT population: DPP	-8,531	28,300	9,212	14
Obesity/diabetes/IGT population: DPS	793	14,461	11,852	3
Obesity/diabetes/IGT population: Other	-433	1,794	818	4
General	-2,677	37,862	4,026	25
Other	-3,657	9,357	556	4
Malnourished	87	900	581	3
Total	**-8,531**	**37,862**	**4,456**	**69**
iNMB categorized by authors' conclusion about cost-effectiveness				
Cost-effective (yes) or sometimes (cost-effective answer)	-2,053	37,862	6,169	47
Not cost-effective (no) or sometimes (not cost-effective answer)	-3,657	268	-940	15
iNMB categorized by concept				
Biological concept	-1,226	1,215	135	6
Psychological concept	-8,531	28,300	4,443	60
Combination of concepts	900	37,862	13,366	3

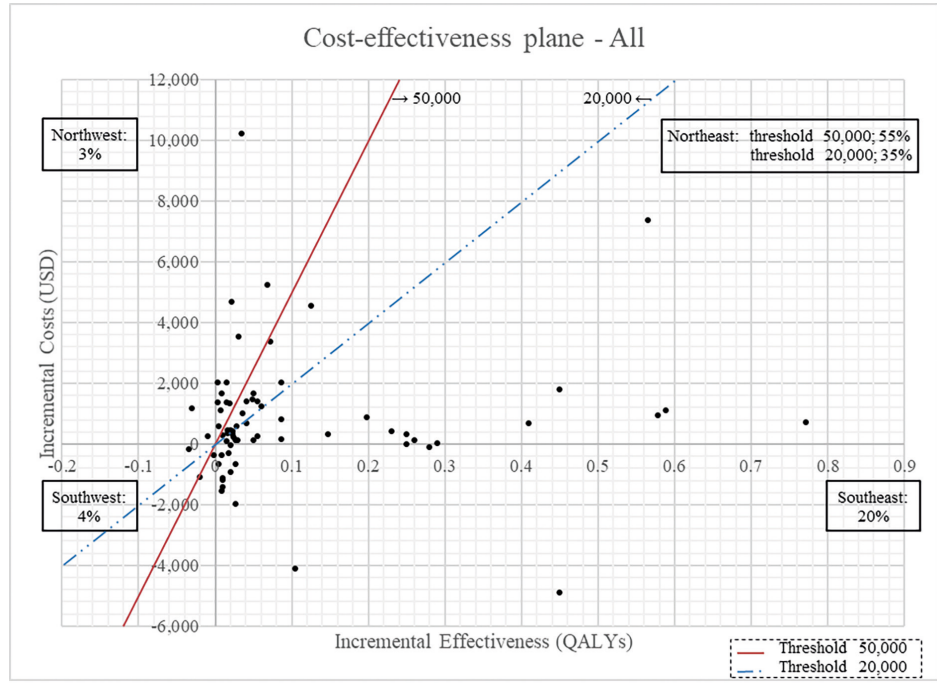
DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; IGT, Impaired glucose tolerance; iNMB, incremental Net Monetary Benefit; WTP, willingness to pay

Results of the CEAs

Appendix 2.6 shows results of the base-case analysis in the different studies but only shows results of comparisons involving an intervention with a PN component. Several comments can be made about these results. First, an overall range in incremental QALYs of -0.034 (158) to 0.77 (150) was found. The smallest QALY gain was seen in the malnourished population (maximum:0.020 QALYs (165)), which is lower than that seen in other populations. Second, authors of 47% (n=27) of the studies concluded that the intervention was cost-effective, 12% (n=7 (106,126,130,131,138,142,146)) concluded that the intervention was not cost-effective, 11% considered the intervention cost-effective in some subgroups (sometimes) (n=6 (128,129,133,135,141,156)) and 30% (n=17 (105,107,112,114,119,132,136,139,140,149,155,157,158)) had no conclusion.

Figure 2.3A shows incremental costs (in 2019 US$) and QALYs of all CUAs in a cost-effectiveness plane. Fifty-five percent of the ICURs are found in the southeast (lower costs, higher QALYs) (20%) or northeast quadrant (higher costs, higher QALYs) below the WTP threshold of $20,000 (35%). This means that 55% of the ICURs can be considered cost-effective given a threshold of $20,000. Using a threshold of $50,000 increases the percentage to 75%. The variation in incremental costs and QALYs seen in Figure 2.3A leads to a range in iNMB (**λ=**50,000) of $-8,531 (114) to $37,862 (150) (mean: $4,456). Table 2.1 provides results of the additional analyses with the iNMB. Appendix 2.7 provides all (converted) costs/ICURs.

A



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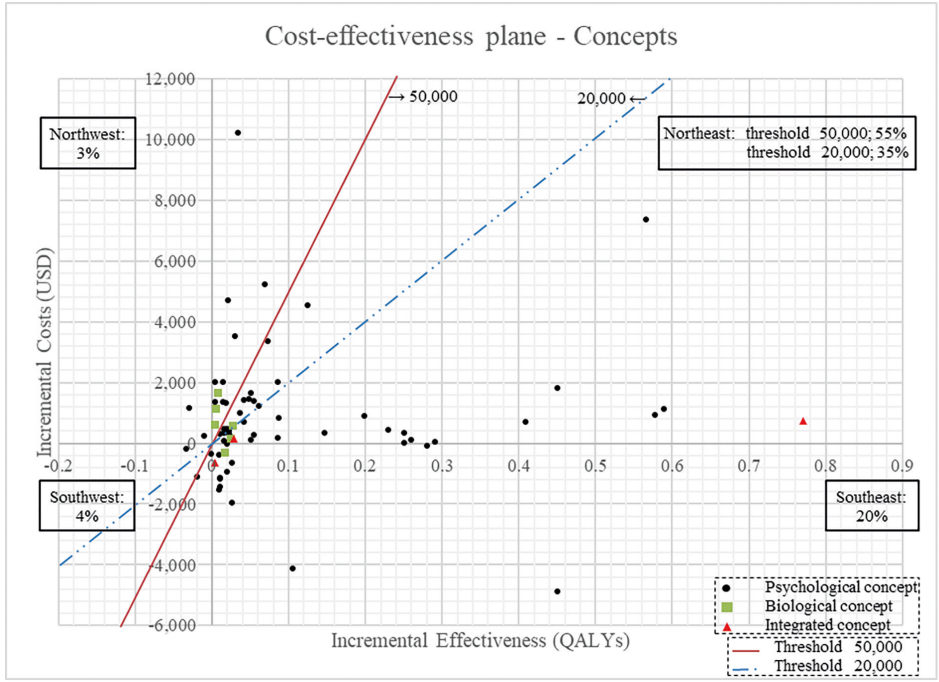

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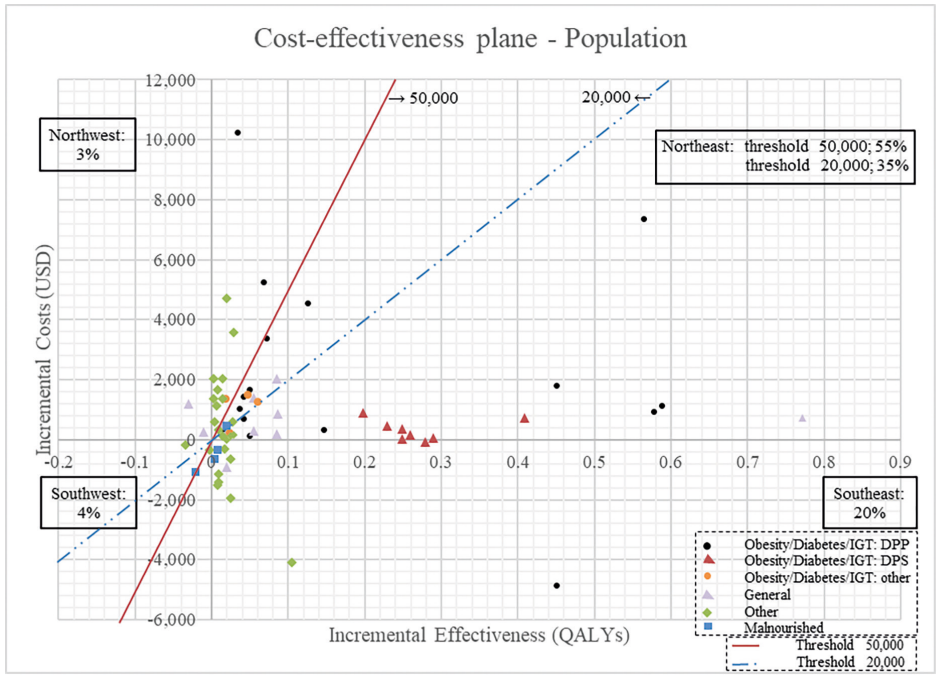


Figure 2.3: Cost-effectiveness plane. QALYs, Quality-Adjusted Life Years; USD; United States dollar. Incremental costs (in 2019 USD) on the y-axis and incremental effects (in QALYs) on the x-axis. Four different cost-effectiveness thresholds (in USD) are shown. The percentages in the northwest, southwest, and southeast quadrants are based on the number of ICURs found in that quadrant. The percentages in the northeast quadrant are based on the number of ICURs below a particular threshold divided by the total number of ICURs in the northeast quadrant. Figure A provides the ICURs of all studies, Figure B shows the ICURs arranged according to the concepts of personalized nutrition used in the studies, and Figure C shows the ICURs according to the population that was studied.

Relationship Between Study Characteristics, Methods, and Results

Examination of the relationship between study features and economic outcomes yielded a number of noteworthy findings. First, interventions that were considered cost-effective according to the authors showed incremental QALYs that varied from 0.0090 (129) to 0.7714 (150) and costs varying from $-4,877 (116) to $7,369 (116) (iNMB (**λ**=$50,000) mean: $5,769) (Table 2.1). In contrast, interventions considered not cost-effective by the authors showed incremental QALYs varying from -0.0340 (129) to 0.0200 (135) and costs from $-1,087 (141) to $2,026 (130) (iNMB (**λ**=$50,000) mean: $-940).

Second, variation in incremental costs, QALYs, and iNMB is seen between the PN concepts (Figure 2.3B). The highest mean iNMB (**λ**=$50,000) was found in the integrated approach ($13,366), followed by the psychological concept ($4,443) and the biological concept ($13) (Table 2.1). Third, a wide variation in incremental costs and QALYs is found within the DPP and DPS interventions, despite their comparable PICOs (Figure 2.3C). For example, 2 main outliers were found in the DPP CUAs; 1 study was associated with relatively high costs ($10,242) and low QALY gain (0.034) ($299,424 per QALY, iNMB (**λ**=$50,000) $-8,531) (114) and the other outlier reported costs of $-4,877 and QALY gain of 0.4500 (iNMB (**λ**=$50,000) $27,377) (116).

The relationship between costs and QALY results of DPP and DPS CUAs and various study characteristics, including methodology, was explored. First, some differences in PICOs of DPS studies might explain differences in outcomes (see Appendix 2.3); slightly different populations were studied in different countries (e.g., Switzerland (109) and the United Kingdom (119)). Moreover, different comparators were used, but no clear pattern related to outcomes was observed here. Second, longer time horizons were associated with more QALY gain. Third, we found that an assumed prolonged effect of DPS intervention (158) (for 20 years) causes higher QALY gain compared to waning or no lasting effect. Fourth, 1 study did not consider the DPS intervention impact on hypertension, hypercholesterolemia, and CVD and reported lower QALYs than other CUAs (119). See Appendix 2.5 for information about modeling approaches of DPP/DPS studies and Appendix 2.8 for the cost-effectiveness planes divided by different characteristics of DPP/DPS interventions.

The model-based DPP CUAs also showed that longer time horizons in the models resulted in more QALY gain. Moreover, much variation was seen in incremental QALYs and costs of CUAs by Herman et al. (116) and Eddy et al. (114) These differences might be explained by

different assumptions. First, Herman et al. (116) used a 70-year time horizon and studied 1 intervention over time, whereas Eddy et al. (114) used a 30-year time horizon and added another intervention after a person was diagnosed with diabetes. Second, both studies assumed a treatment waning effect. However, Eddy et al. (114) did not assume a constant transition rate, resulting in less cost-savings than Herman et al. (116). Third, Eddy et al. (114) incorporated a considerably higher level of biological detail and clinical realism which affected the outcomes.

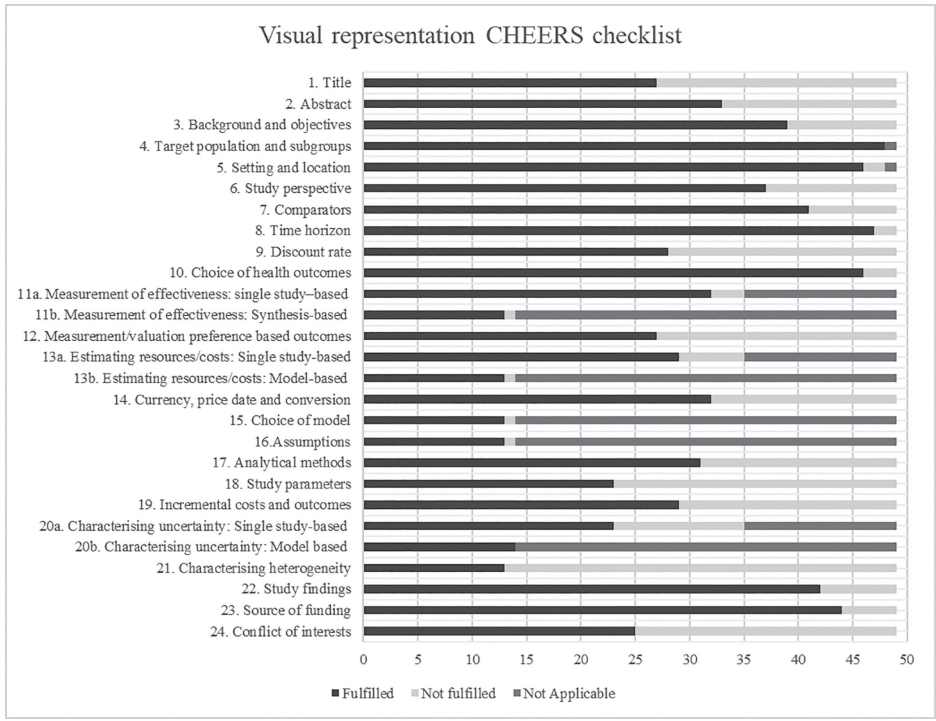


Figure 2.4: Study quality based on the CHEERS checklist (102). CHEERS, Consolidated Health Economic Evaluation Reporting Standards. The 24 statements of the checklist are shown on the y-axis. The frequencies of each category are shown on the x-axis. Three categories were used: Fulfilled (study scored well on this statement), Not fulfilled (study scored poorly) and Not Applicable (i.e. the statement was not applicable for a study). The total number of studies included was 49 since the article of Dalziel et al. was counted as 1 study.

Quality of Economic Analyses

Figure 2.4 summarizes the quality of reporting using the CHEERS checklist (102). Many studies showed a high quality of reporting their results, but 6 studies (134,140,149,151,152,167) reported 10 or fewer statements correctly. Most problems in reporting were found in statement 18 related to study parameters (n=26 not fulfilled) and in reporting heterogeneity of cost-effectiveness results across different subgroups/patient populations (statement 21);13 studies (107–112,114,116,117,128,129,141,144) reported this appropriately. Appendix 2.9 provides information about the quality per study.

DISCUSSION

This systematic literature review was done to synthesize and critically appraise CEAs of PN interventions. We identified 53 CEAs of interventions with a PN component in adults. Interventions were based mostly on the psychological concept of PN (48 studies), 1 study (128) on the biological concept and 4 studies (140,144,150,166) on the integrated approach. Approximately half of the authors concluded that an intervention with a PN component was cost-effective (47%). Of the interventions that reported a QALY gain, 55% were cost-effective according to the lowest assessed threshold $20,000, increasing to 75% based on a threshold of $50,000. Moreover, studies that used an integrated approach showed the highest iNMB based on both $50,000 and $20,000 thresholds.

Wide variation in methodology of the CEAs in this review was found. First, variation is seen in terminology/definitions of PN and in the conceptualization of the terms. For example, Sherwood et al. (107) used “individualized” to describe individual counseling sessions with goal-setting and individual feedback, whereas Olsen et al. (111) only used “individualized” to describe individualized counseling sessions. Furthermore, the duration of the personalized component used in the interventions varied. For example, 2 studies used the term “personalized” but varied the duration of the interventions; participants receiving 1 intervention could expect to have 4 counseling sessions on personalizing snacks (134) whereas participants receiving a different intervention received personalized messages via the internet when needed (106). Future research could examine how the different terms used in PN relate to cost-effectiveness.

Second, different comparators and number of comparators are used in studies, resulting in different cost-effectiveness outcomes. While the “best” comparator is study-dependent, 1 comparator might be insufficient in some cases. For example, if usual care is used as a comparator to assess a PN intervention, a second comparator could be a similar nutrition intervention but without the personalized component. By adding this third arm, researchers would be able not only to see the effect of the intervention (when compared to usual care), but also the effect of a specific personalized component. Additional research regarding the best choice of comparator when studying PN interventions is needed.

Third, different cost perspectives were used; choice is mainly depending on the resident country of the population. Two CEAs found in this review used the perspective of an individual (114,142), which might be considered when assessing the cost-effectiveness of PN interventions since individuals will likely have to pay for at least part of the extra costs; the actual amount would be country- and intervention-dependent. However, these 2 CEAs did not include all costs related to this perspective. This is very similar to what Bilvick Tai et al. (168) reported in their systematic review. They not only found a paucity of CEAs using a patient perspective but also observed that studies that used this perspective did not fully explore the true patient costs.

Fourth, variation was observed in time horizons and many CEAs used time horizons that are probably too short to capture all important effects of PN interventions on outcomes and costs. That is, CEAs with a short follow-up would not observe any long-term benefits of behavioral change and would therefore show less favorable results than ones with a longer follow-up (158,169). Furthermore, nutrition often has a preventive effect, in which benefits take longer timespans to develop (170). One CEA from this review supports this and showed a decrease in ICURs when time horizons increase (per QALY gained: £113,905 ($238,856) (year 1) to £5,825 ($12,215) (year 15)) (119). Moreover, from DPP/DPS studies it was observed that longer time horizons were associated with more QALY gain. It is therefore recommended to use longer time horizons and/or to include both trial and model data to investigate the full impact of PN. While well-designed trials can help to establish short-term (cost-)effectiveness of interventions, modeling beyond that point may be unavoidable to estimate the intervention's overall cost-effectiveness.

It is debatable what the best modeling approach for PN interventions beyond the trial can be. Nutrition economics requires a holistic approach because of the complexity of food and its interactions with multiple interdependent processes (170) and yet there is no systematic approach to assess the health impact of (personalized) nutrition (171). Therefore, there is still much variation in models for PN (even those with comparable PICOs, e.g., DPP/DPS interventions), resulting in avoidable variation in estimated costs and QALYs. Some suggestions specific for nutrition interventions could be made for models, such as linking identified markers in trials to longer-term outcomes (170). For example, Eddy et al. (114) linked LDL cholesterol to a reduction in long-term CVD risk. More research is needed to define good PN modeling approaches.

Variation in QALYs was observed between populations. The smallest QALY gain was observed in the malnourished population. Since all studies found in this population were done in elderly, this might explain the lower QALY gain compared to younger populations. These findings are in line with an earlier review that reported that studies in elderly found no differences in quality of life between intervention and control treatments (172).

Additionally, variations in health economic outcomes between the different PN concepts were found, in which most promising outcomes were found by the integrated approach. However, only a few CEAs with different methodologies evaluated the integrated approach. Nevertheless, there are different reasons to suspect that an integrated approach will be most cost-effective. First, this review found a lowest iNMB in CEAs with an integrated approach. Second, previous studies in the nutrition field have mentioned that an integration of biological and psychological characteristics is the optimal approach (23,97,173). An example of an intervention with an effective integrated approach is Food4Me, which has shown greater improvement in dietary behavior (38,174). Moreover, CEAs of integrated approaches in different disease areas often tend to have positive results, such as improved cost-effectiveness of the

integrated care management versus the standard care of advanced chronic obstructive pulmonary disease (175). This integrated approach of PN deserves further investigation.

Limitations

First, since our literature search was restricted to CEAs published in English-language journals, it may have missed CEAs reported elsewhere. Second, some bias in our review might have arisen through inclusion of poor-quality CEAs. Nevertheless, assessing quality of the CEAs was important for revealing improvements for future CEAs, such as better reporting on study parameters. Third, our results could have been influenced by publication bias, since interventions that are found to be cost-effective are more likely to be published (176). Fourth, heterogeneities in methodology and the limited number of CEAs that studied the integrated or biological concept, made it difficult to draw stable conclusions about the cost-effectiveness of these concepts; more CEAs are therefore needed.

Future Research

In addition to the suggestions for future research already given above, another question to consider is how much people are willing and able to spend on PN. This review calculated iNMBs with 2 different WTP thresholds, but there is no specific cut-off point defined in the literature for PN (135). A study by Corso et al. (177) found that treatment is preferred above prevention by society, which might imply that the WTP might be greater for a comparable treatment rather than for prevention-oriented PN. Since costs of these interventions are often (partly) borne by the user, WTP studies of PN interventions could give perspectives on potential consumer behavior for 2 reasons. First, a WTP will indicate the willingness of the user to make the required behavioral change and how much the user expects to benefit from PN. Second, these studies show policy makers how much demand might vary between different social classes and indicate how demand for PN varies depending on the level of public subsidy applied. However, to date, it seems there has been only 1 published WTP study in this area (178).

Moreover, multiple criteria decision analysis might be considered for future research, because there are many factors besides cost-effectiveness that affect the value of PN (120,179–181). Personal preferences might be relevant as well, and particularly for diet-related interventions since food —and all activities related to food—has a profound role in a person's life. Therefore, any assessment of the merits of PN strategies should consider preferences.

CONCLUSIONS

Heterogeneity exists in the methodology of CEAs done in the field of PN, including variation in definitions and its conceptualization, PICOs and modeling approaches. This leads to differences in health economic outcomes. Nevertheless, PN interventions tend to be cost-effective compared to usual care and drug-related treatments with WTP thresholds of $20,000 and $50,000. This suggests that many PN interventions may offer good value for money. Moreover,

this review found that an integration of PN concepts may yield the greatest iNMB. Future CEAs should improve their methods to support later implementation and reimbursement decisions.

APPENDICES

Appendix 2.1: Search terms used in the different bibliographic databases

embase.com

('cost effectiveness analysis'/de OR 'economic evaluation'/de OR 'cost benefit analysis'/de OR 'cost utility analysis'/de OR 'program cost effectiveness'/de OR economics/de OR 'health economics'/de OR 'economic aspect'/de OR (((cost OR costs) NEAR/3 (effectiv* OR efficien* OR benefit* OR utilit* OR quality-of-life OR qol OR hrqol)) OR Econom*):ab,ti) AND ('diet therapy'/exp OR 'dietary supplement'/exp OR supplementation/de OR 'Mediterranean diet'/de OR 'low calorie diet'/exp OR 'low carbohydrate diet'/exp OR 'healthy diet'/de OR 'gluten free diet'/de OR 'nutrition education'/de OR 'probiotic agent'/de OR 'lifestyle'/exp OR 'lifestyle modification'/de OR 'body weight loss'/exp OR (((diet* OR nutrition*) NEAR/3 (therap* OR Interven* OR modif* OR restrict* OR coach* OR low-energ* OR low-carb* OR low-calor* OR low-fat* OR low-salt* OR low-protein* OR ketogenic* OR support* OR consult* OR gluten OR weight-loss OR Mediterran* OR education* OR healthy OR counsel* OR management* OR habit*)) OR snack* OR ((supplement* OR fortif*) NEAR/3 (nutrition* OR diet* OR calcium OR vitamin* OR multivitamin* OR fatty-acid OR food OR energ* OR iron OR selenium OR folate* OR folic-acid OR nutrient* OR micronutrient* OR multimicronutrient* OR macronutrient* OR multimacronutrient* OR iodine* OR feed OR zinc OR omega OR fiber* OR fibre* OR protein*)) OR probiotics* OR synbiotics* OR ((sodium OR salt OR fat) NEAR/6 (reduc* OR restrict*) NEAR/6 (diet* OR interven* OR intake*)) OR ((fruit OR vegetable) NEAR/3 intake*) OR lifestyle OR life-style OR ((weight OR bodyweight) NEAR/3 (loss* OR losing OR reduc* OR change OR management*)) OR (Calor* NEAR/3 Restrict*)):ab,ti) AND ('personalized medicine'/de OR (personali* OR individuali* OR precision* OR ((stratif* OR tailor* OR targeted*) NEAR/6 (nutrition* OR diet* OR lifestyle OR life-style OR therap* OR intervention* OR treatment*)) OR (individual NEXT/1 (treatment OR therapy))):ab,ti) NOT ([Conference Abstract]/lim) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT (juvenile/exp NOT adult/exp)

Medline ovid

(Cost-Benefit Analysis/ OR Economics/ OR Economics, Medical/ OR (((cost OR costs) ADJ3 (effectiv* OR efficien* OR benefit* OR utilit* OR quality-of-life OR qol OR hrqol)) OR Econom*).ab,ti.) AND (exp Diet Therapy/ OR diet therapy.fs. OR exp Dietary Supplements/ OR supplementation/ OR Diet, Mediterranean/ OR Caloric Restriction/ OR Diet, Carbohydrate-Restricted/ OR Healthy Diet/ OR Diet, Gluten-Free/ OR Diet, Reducing/ OR Probiotics/ OR Life Style/ OR exp Weight Loss / OR (((diet* OR nutrition*) ADJ3 (therap* OR Interven* OR modif* OR restrict* OR coach* OR low-energ* OR low-carb* OR low-calor* OR low-fat* OR low-salt* OR low-protein* OR ketogenic* OR support* OR consult* OR gluten OR weight-loss OR Mediterran* OR education* OR healthy OR counsel* OR management* OR habit*)) OR snack* OR ((supplement* OR fortif*) ADJ3 (nutrition* OR diet* OR calcium OR vitamin* OR multivitamin* OR fatty-acid OR food OR energ* OR iron OR selenium OR folate* OR folic-acid OR nutrient* OR micronutrient* OR multimicronutrient* OR macronutrient* OR multimacronutrient* OR iodine*

OR feed OR zinc OR omega OR fiber* OR fibre* OR protein*)) OR probiotics* OR synbiotics* OR ((sodium OR salt OR fat) ADJ6 (reduc* OR restrict*) ADJ6 (diet* OR interven* OR intake*)) OR ((fruit OR vegetable) ADJ3 intake*) OR lifestyle OR life-style OR ((weight OR bodyweight) ADJ3 (loss* OR losing OR reduc* OR change OR management)) OR (Calor* ADJ3 Restrict*)).ab,ti.) AND (Precision Medicine/ OR (personali* OR individuali* OR precision* OR ((stratif* OR tailor* OR targeted*) ADJ6 (nutrition* OR diet* OR lifestyle OR life-style OR therap* OR intervention* OR treatment*)) OR (individual ADJ (treatment OR therapy))).ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) NOT (juvenile/ NOT adult/)

Web of science

TS=(((((cost OR costs) NEAR/2 (effectiv* OR efficien* OR benefit* OR utilit* OR quality-of-life OR qol OR hrqol)) OR Econom*)) AND ((((diet* OR nutrition*) NEAR/2 (therap* OR Interven* OR modif* OR restrict* OR coach* OR low-energ* OR low-carb* OR low-calor* OR low-fat* OR low-salt* OR low-protein* OR ketogenic* OR support* OR consult* OR gluten OR weight-loss OR Mediterran* OR education* OR healthy OR counsel* OR management* OR habit*)) OR snack* OR ((supplement* OR fortif*) NEAR/2 (nutrition* OR diet* OR calcium OR vitamin* OR multivitamin* OR fatty-acid OR food OR energ* OR iron OR selenium OR folate* OR folic-acid OR nutrient* OR micronutrient* OR multimicronutrient* OR macronutrient* OR multimacronutrient* OR iodine* OR feed OR zinc OR omega OR fiber* OR fibre* OR protein*)) OR probiotics* OR synbiotics* OR ((sodium OR salt OR fat) NEAR/5 (reduc* OR restrict*) NEAR/5 (diet* OR interven* OR intake*)) OR ((fruit OR vegetable) NEAR/2 intake*) OR lifestyle OR life-style OR ((weight OR bodyweight) NEAR/2 (loss* OR losing OR reduc* OR change OR management*)) OR (Calor* NEAR/2 Restrict*))) AND ((personali* OR individuali* OR precision* OR ((stratif* OR tailor* OR targeted*) NEAR/5 (nutrition* OR diet* OR lifestyle OR life-style OR therap* OR intervention* OR treatment*)) OR (individual NEAR/1 (treatment OR therapy)))) NOT ((child* OR infan* OR adolescen*) NOT (adult*))) AND DT=(article) AND LA=(english)

Cochrane CENTRAL

((((cost OR costs) NEAR/3 (effectiv* OR efficien* OR benefit* OR utilit* OR quality-of-life OR qol OR hrqol)) OR Econom*):ab,ti) AND ((((diet* OR nutrition*) NEAR/3 (therap* OR Interven* OR modif* OR restrict* OR coach* OR low-energ* OR low-carb* OR low-calor* OR low-fat* OR low-salt* OR low-protein* OR ketogenic* OR support* OR consult* OR gluten OR weight-loss OR Mediterran* OR education* OR healthy OR counsel* OR management* OR habit*)) OR snack* OR ((supplement* OR fortif*) NEAR/3 (nutrition* OR diet* OR calcium OR vitamin* OR multivitamin* OR fatty-acid OR food OR energ* OR iron OR selenium OR folate* OR folic-acid OR nutrient* OR micronutrient* OR multimicronutrient* OR macronutrient* OR multimacronutrient* OR iodine* OR feed OR zinc OR omega OR fiber* OR fibre* OR protein*)) OR probiotics* OR synbiotics* OR ((sodium OR salt OR fat) NEAR/6 (reduc* OR restrict*) NEAR/6 (diet* OR interven* OR intake*)) OR ((fruit OR vegetable) NEAR/3 intake*) OR lifestyle OR life-style OR ((weight OR bodyweight) NEAR/3 (loss* OR losing OR reduc* OR change OR management*)) OR (Calor* NEAR/3 Restrict*)):ab,ti) AND ((personali* OR individuali* OR precision* OR ((stratif* OR tailor*

OR targeted*) NEAR/6 (nutrition* OR diet* OR lifestyle OR life-style OR therap* OR intervention* OR treatment*)) OR (individual NEXT/1 (treatment OR therapy))):ab,ti)

Google scholar

“cost|costs effectiveness|efficiency|benefit|utility” “diet|dietary|nutrition|nutritional therapy-|Intervention|restriction”|”energy|carb|carbohydrates|calory|fat|salt|protein|ketogenic diet” personalized|personalised|individualized|individualised|precision

Appendix 2.2: Inclusion and exclusion criteria (sequence reflects the order in which they were applied)

Order	Exclusion criteria (see figure 2.1)	Related inclusion criteria	Explanation	
1.	Non-English/ No-full text/other publication type/ Protocol/ Systematic review	English full-text articles when no systematic review	General features that the full-text article needed to fulfill. If it was a non-English article, another type of publication (e.g. abstract or supplement), a protocol or a duplicate article or a systematic review of CEAs, it was excluded. However, all systematic reviews were manually checked for any articles that met the inclusion criteria.	
2.	Not a cost-effectiveness analysis	Cost-effectiveness analysis	A cost-effectiveness analysis included all types of full economic evaluations.	
3.	No nutrition component	Nutrition component	The study had to involve an intervention with a nutrition component; other personalized interventions were excluded.	
4.	No personalized nutrition intervention	Personalized	No personalized nutrition component. This mean excluded an intervention if it only consisted of a general nutrition component and was not personalized (based on the definition of personalized nutrition by Ordovas et al. (23).	
5.	No adults (only children)	Interventions focusing on adults (or adults and children).	Studies solely focusing on children were excluded because of inherent differences between adults and children, including factors relating to motivation, responsibilities, needs and their environment), which might lead to different intervention characteristics and heterogeneity in cost-effectiveness outcomes (182).	
6.	Underweight	Interventions that focused on normal, pre-obesity or obese were included. Underweight was excluded.	Classification of adult underweight, overweight and obesity according to BMI (183):	
			Classification:	***Measurement (kg/m2):***
			Underweight	<18.5
			Normal weight	18.5 – 24.9
			Pre-obesity	25.0 – 29.9
			Obese Obesity class I Obesity class II Obesity class III	≥ 30.00 30.0-34.9 35.0-39.9 ≥ 40
7.	Clinical nutrition	No clinical nutrition	Clinical nutrition comprises nutrition devices targeted for medical use and which involves something that is prepared by the industry, such as enteral nutrition.	

BMI, Body Mass Index; kg, kilogram; m; meter.

Appendix 2.3: General characteristics of the selected studies

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
Obesity/Diabetes/IGT population: DPP intervention																			
Ackermann et al. 2006 (112)	Adults with IGT (>25 years) and a BMI of 24 kg/m2	DPP lifestyle	x	x	x			2	Ind. Couns.	x		x	x			Standard lifestyle recommendations	Healthpayer	Lifetime	Model/CUA
Caro et al. 2004 (113)^	Canadian individuals with IGT	(1) Acarbose			x			4								No intervention	Healthcare payer	10 years	Model/CEA
		(2) Intensive lifestyle modification program	x	x	x				Ind. Couns	x		x	x						
		(3) Metformin			x														

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Eddy et al. 2005(114)	Adults at high risk for diabetes	(1) DPP lifestyle	x	x	x			4	Ind. Couns.	x		x	x			Basis: none. When diabetes: dietary advice. HbA1c> 7%: intensive management program.	Patient, health plan, societal	30 years	Model/CUA
		(2) Lifestyle when FPG level > 125 mg/dL	x	x	x				Ind. Couns.	x		x	x						
		(3) Metformin			x														
Herman et al. 2005 (116)	Members of the DPP cohort (>25 years) with IGT	(1) Intensive lifestyle DPP	x	x	x			3	Ind. Couns.	x			x	x		Placebo	Health system and societal	Lifetime	Model/CUA
		(2) Metformin DPP			x														
Icks et al. 2007 (131)	People (60–74 years) with a BMI ≥24 kg/m2 and prediabetes status	(1) Metformin DPP			x			3								No intervention	Statutory health insurance and societal	3 years	Model/CEA
		(2) Lifestyle DPP	x	x	x				Ind. Couns. tailored to each subject.	x		x	x						

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Palmer et al. 2004 (108)	Resemble study population of the DPP (50.6 years; 94.2 kg; BMI 34.0 kg/m2; men, 32.2%)	(1) Metformin DPP			x			3								Placebo and standard advice diet and PA	Third-party reimbursement payer's	Lifetime	Model/CEA
		(2) Lifestyle DPP	x	x	x				Ind. Couns. tailored to each person	x		x	x						
Ramachandran et al. 2007 (115)	Adults (35–55 years) with reproducible IGT	Indian DPP: (1) Lifestyle modification	x	x	x		x	4	Ind. Couns.	x			x	x		Standard healthcare advice	Healthcare system	3 years	Trial/CEA
		(2) Metformin			x														
		(3) LSM & metformin combined	x	x	x		x		Ind. Couns.	x			x	x					
Smith et al. 2016 (153)	Overweight / obese cohort (some with diabetes) and >1 weight related CVD risk factor.	Online adaptation of DPP.		x		x		2	Ind. Couns.	x			x			Usual care	Healthcare and societal	10 years	Model/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
The Diabetes prevention program. 2003 (104)	Participants with IGT (>25 years), a BMI > 24 kg/m2 (22 kg/m2 for Asian Americans)	(1) Lifestyle DPP	x	x	x			3	Ind. Couns.	x		x	x			Placebo	Health system and Societal	3 years	Trial/CEA/ CUA
		(2) Metformin DPP			x														
Obesity/Diabetes/IGT population: DPS intervention																			
Avenell et al. 2004 (119)	Overweight persons (20-65 years) with IGT	Finnish DPS	x	x	x			2	Ind. Couns. tailored to each subject	x		x	x			Oral and written diet/ exercise information at baseline	Healthcare purchaser	6 years (15 years sensitivity analysis)	Model/CUA
From Dalziel et al. (158): Eriksson et al. 1999 (127)	Overweight subjects (BMI > 25 kg/m2) (40-64 years) and with IGT.	Finnish DPS: Physician and nutritionist advice about risk factors for diabetes and weight loss goal + exercise session.	x	x	x			2	Tailored face-to face dietary advice	x		x	x			General dietary advice	Societal	6 years/ 20 years	Trial/ Model; CEA/CUA
Galani et al. 2007 (109)	Obese/overweight people (>25 years)	Finnish DPS (Lifestyle)	x	x	x			2	Ind. Couns.	x		x	x			Standard care	Societal	Lifetime	Model/ CEA/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
Lindgren et al. 2007 (118)	Patients (60 years) with IGT	DPS lifestyle	x	x	x			2	Ind. Couns.	x			x		x	Control	Societal	6 years	Model/CUA
Obesity/Diabetes/IGT population: other interventions																			
Barton et al. 2009 (125)	Adults (≥45 years) with self-reported knee pain and BMI ≥28	(1) Dietary intervention plus quadriceps strengthening exercises	x	x	x			4	Pers. dietary plan	x				x		Best alternative	Healthcare	2 years	Trial/CUA
		(2) Dietary intervention		x	x					x				x					
		(3) Quadriceps strengthening exercises	x		x														
Befort et al. 2010 (142)	Adult female, residence in rural area, BMI between 25-44.9	Group conference call via phone prevention for diet & exercise	x	x			x	2	C:1-on 1 counseling Both I&C: goal-setting.	x					x	One-on-one phone counseling *C= personalized*	Program and Program + patient	6 months	Trial/CEA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
From Dalziel et al.(158): Swinburn et al. 2001 (159)	Participants with glucose intolerance	Intensive education fat reducing strategies. Via diaries and small group sessions.		x	x			2	Pers. goal setting	x				x		Usual diet	Societal	5 years	Trial/ Model; CEA/CUA
From Dalziel et al. (158): Pritchard et al. 1999 (160)	25-65 years with overweight, hypertension or type 2 diabetes	(1) Dietitian: Counseling sessions	x	x	x			3	Ind. Couns. + advice	x			x			Usual care	Societal	1 year	Trial/CEA
		(2) Doctor + dietitian: Counseling sessions + progress measurements	x	x	x				Ind. Couns. + advice	x			x						
Franz et al. 1995 (144)	Non-insulin-dependent diabetes mellitus (NIDDM) adults	Practice guidelines nutrition care: MNT; nutrition prescription and educational interventions.		x	x			2	Ind. Couns. / tests	x	x		x			Basic nutrition care	Health-care organization	6 - months	Trial/CEA
Glasgow et al. 1997 (145)	Adults (>40 years) having diabetes attending an internal medicine outpatient clinic visit	Medical office-based intervention focused on dietary self-management.		x	x	x	x	2	Ind. goal setting + plan.	x			x			Usual care	Health-care organization	1 year	Trial/CEA
Goldfield et al. 2001 (146)	Families with obese children (8-12 years)	Mixed treatment (group and Ind. sessions): Identify behaviors influencing weight changes, goals and feedback. Treatment components both I&C: diet, physical activity, self-monitoring, stimulus control.	x	x	x			2	Individual sessions, identifying behaviors.	x			x			Group sessions only	-	1 year	Trial/CEA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Kaplan et al. 1987 (105)	Non-insulin-dependent diabetes mellitus (NIDDM) adults	(1) Diet (10w): behavior modification approaches (nutritional advice counseling)		x	x			4	Ind. Couns.	x			x			10 didactic sessions	-	1.5 years	Trial/CUA
		(2) Exercise (10w)	x		x														
		(3) Diet +exercise: both arms (10w)	x	x	x				Ind. Couns.	x			x						
McConnon et al. 2007 (106)	Obese adults (18-65 years) with internet access	Website providing Pers. advice, tools and information supporting behavior change.	x	x		x		2	Pers. messages via internet	x				x		Usual care	Societal	1 year	Trial/CUA
Olsen et al. 2005 (111)	GPs refer or give advice themselves. Patients BMI (≥30 kg / m2), waist circumference (men > 102cm; women > 88cm), dyslipidemia or type2 diabetes	Individual counseling by dietitian based on the indication for referral by GP, dietary history and diet routines.	x	x	x			2	Ind. Couns.	x			x			Usual care: GP counseling (general advice)	-	1 year	Trial/CEA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Redman et al. 2017 (151)	Pregnant women (age 18-40 years) who were overweight or obese	SmartMoms: weight management program: (1) In-person	x	x	x			3	I based on weight, data -driven feedback, Ind. advice / coach	x			x			Usual care	-	Not clear, probably 26 weeks.	Trial/CCA
		(2) Via mobile phone	x	x			x			x			x						
Segal et al. 1998 (110)	(1) Seriously obese	I: Intensive diet and behavioral modification		x	x			6 + (C each arm)	Ind. Couns.	x			x			Control for each program	-	25 years	Model/CEA
	(2) Women with previous gestational diabetes	II: Intensive diet + behavioral modification		x	x				-										
	(3) Seriously obese	III: Surgery for severe obesity			x														
	(4) Overweight men	IV: Group behavioral modification	x	x	x														
	(5) High risk adults	V: General practitioner advice	x	x	x														
	(6) General population	VI: Media campaign + community support				x													

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;- CEA/CUA/CBA/CCA)
Sherwood et al. 2006 (107)	Overweight adults managed care organization members	10 lessons with health counselor: instructional material describing a rationale for specific behavior change strategy, goals related and homework. (1) Mail: only mail contact; progress reports	x	x		x		3	Ind. Couns. / goal setting / feedback	x			x			Usual care	-	2 years	Trial/CEA
		(2) Phone: calls to provide feedback. Individual follow-up on preferred topics.	x	x			x			x			x						

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;- CEA/CUA/CBA/CCA)
Toobert et al. 2007 (155)	Postmenopausal women with type 2 diabetes	Mediterranean Lifestyle program, with motivational techniques. After 6 months: (a) Faded schedule of weekly meetings (b) 4 meetings over 18 months with project staff to complete a Pers. computer-assisted program.	x	x	x	x		2	Personal goals/support Ind. recommendations/rewards	x			x	x		Usual care	Potential payer	2 years	Trial/CEA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Wylie-Rosett et al. 2001 (157)	BMI > 25 kg/m2 in a freestanding health maintenance organization, and 1 CVD risk factor	Cognitive behavioral approach for tailoring lifestyle modification goals: (1) Workbook alone	x	x				4								Control	Managed care organization	1 year	Trial/CEA
		(2) Workbook+-computerized tailoring using computer kiosks with touch screen monitors	x	x		x			Ind. needs assessment, Computerized tailoring, Tailored goals	x		x	x						
		(3) Workbook+-computer+staff consultation	x	x	x	x			Same as (2)	x		x	x						

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
General/Healthy population																			
From Dalziel et al. (158): de Lorgeril et al. 1999 (150)	Individuals (<70 years), clinically stable, and no medical or social conditions that would limit their ability to participate in a dietary trial	Mediterranean diet with session, Pers. instruction, evaluation and plasma fatty acids were analyzed as objective biomarkers.		x	x			2	Pers. instructions, Detailed/customized to each individual	x	x			x	x	Western diet	Societal	46 months / 20 years	Trial/CEA/Model/CUA
From Dalziel et al. (158): Steptoe et al. 2003 (137)	Individuals (18-70 years) without serious illness	Behavioral counseling on nutrition tailored to individual with Pers. advice and goal setting.		x				2	Ind. Couns. Tailored to individual Pers. Advice / goal setting	x		x	x	x		Nutrition education	Societal	1 year/20 years	Trial/CEA/Model/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
Leigh et al. 1992 (149)	Bank of America retirees	Senior healthcare program: lifestyle questionnaires, serial personal health risk reports, Ind. recommendation letters, newsletters and a self-management book.	x	x		x		2	Ind. recommendation letters	x			x	x		Questionnaire only	-	1 year	Trial/CEA
Lindgren et al. 2003 (117)	Men (35-60 years): no previous cardiovascular disease, diabetes, or other severe illnesses.	(1) Dietary advice		x	x			4	Ind. Couns.	x			x			No intervention	Healthcare payer and societal	Lifetime	Model/ CEA/CUA
		(2) Exercise	x		x														
		(3) Combination		x	x				Ind. Couns.	x			x						
Schulz et al. 2014 (135)	Adults (18-65 years)	Web-based computer-tailored multisession program: advice about unhealthy behavior. (1) Sequential	x	x		x		3	Pers. advice	x		x		x		Only health risk appraisal	Societal	2 year	Trial/CEA/ CUA
		(2) Simultaneous	x	x		x				x		x		x					

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/ model;- CEA/CUA/ CBA/CCA)
Sukhanova et al. 2009 (154)	Current members of participating HMO (21-65 years), no health conditions that prohibited from dietary changes	MENU intervention: (1) Tailored website program		x		x		3	Tailored/ Pers. messages	x		x		x		Untailored website program	-	1 year	Trial/CEA
		(2) Tailored website program + personalized counseling via email (HOBI)							Pers. counseling										
Other population																			
Broekhuizen et al. 2015 (126)	Familial hypercholesterolemia	Lifestyle intervention (PRO-FIT): tailored web-based advice and 1 face to face counselling + telephone booster sessions.	x	x	x	x	x	2	Pers. feedback and counseling	x				x		Usual care	Healthcare	1 year	Trial/CEA/ CUA
Chatterton 2018 (164)	Adults DSM-IV criteria (depression) + reporting poor dietary quality	SMILES trial: dietary support intervention (modified Mediterranean diet).		x	x			2	Pers. advice + counseling	x				x		Intensity matched social support	Health AND societal	12 weeks	Trial/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Emmons et al. 2005 (143)	Patients (40-75 years) had undergone either flexible sigmoidoscopy or colonoscopy at the gastroenterology department	PREVENT Multiple Risk Factor: (a) Motivational + goal-setting phone call (b) 4 follow-up telephone counseling tailored to the patient (c) Computer-generated tailored print progress reports (d) Tailored self-help materials	x	x		x	x	2	Tailored phone call, Guidebook with Pers. Suggestions, Personal diary/goals.	x		x		x		Standard of care	Intervention	8 months	Trial/CEA
Ethgen et al. 2016 (128)	Women (65, 70, 80 years), no increased risk of osteoporosis, or with low bone mineral density, defined as a T-score < 2.5 at spine and/or at femoral neck or with prevalent vertebral fracture	Daily administration of one, two or three portions of a yoghurt fortified with vitamin D. (1) 1 yoghurt		x	x			4	Tailoring on calcium and vitamin D already received		x	x				No supplementation	Belgian healthcare payers (government and patients)	Lifetime	Model/CUA
		(2) 2 yoghurts		x	x						x	x							
		(3) 3 yoghurts		x	x						x	x							

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Gillespie et al. 2017 (129)	Patients with a CHD	SPHERE: (a)Training staff for tailored care plans. (b)Tailored patient care plans: * Initial target setting consultation * Patient held booklet * Regular consultation	x	x	x		x	2	Tailored care plans, Goal identification-Target setting	x		x		x		Existing secondary prevention services (general practice care)	Healthcare provider	6 years	Trial/CUA
Herman et al. 2014 (147)	Postal workers (25-65 years) with increased risk of CVD	Multi-worksite intervention with enhanced usual care and naturopathic care	x	x	x			2	Ind. Couns. /care	x			x			Enhanced usual care	Societal and employer	1 year	Trial/CEA/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Holt et al. 2018 (130)	People with first episode psychosis, schizophrenia or schizoaffective disorder	STEPWISE: (a) Group-based education sessions (b) 1-to-1 support, personalized contact by telephone. Progress and goals discussed. (c) Group booster sessions/ standard info	x	x	x		x	2	Personalized contact	x				x		Usual care: standard written lifestyle information	Health and societal	12 months	Trial/CUA
Price et al. 2006 (134)	Patients (>60 years) admitted to acute orthopedic units with a low trauma fracture of the femoral neck	4 visits by dietitian: 1. Pre-intervention: recording anthropometric measures and preferences/beliefs on nutrition. 2/3. Counseling session: need for nutritional support, personal dietary goals, advice 4. Final: results and nominating 3 snacks that were already pre-sorted based on needs.		x	x			2	Snacks were based on preferences/ needs and individual counseling sessions/ personal goals	x				x		Providing 2 cartons of commercially prepared sip feeds daily	-	4 weeks	Trial/CEA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Sikand et al. 2000 (152)	Men (21-75 years) with combined hyperlipidemia	MNT: with dietitian intervention were the patient's unique eating issued through client-centered counseling.		x	x			2	Client-centered counseling.	x					x	Statin therapy	-	1 year	Trial/CEA
Speed et al. 2010 (136)	People (≥50 years), chronic constipation, had been prescribed laxatives (≥3) in 12 months, or recorded diagnosis of chronic functional constipation	(1) Pers. dietary and lifestyle advice, with reinforcement	x	x	x		x	3	Pers. approach / assessment / information / goals / plan	x			x	x		Standard care	Health service at macro level	3 months	Trial/CUA
		(2) Standardized, non-Pers. dietary and lifestyle advice	x	x	x		x												

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Troyer et al. 2010 (156)	Participants (>60 years) residing in community settings who were medically diagnosed with either hypertension or hyperlipidemia	(1) Therapeutic meal group		x			x	4	Meals were changed based on taste.	x					x	Literature control group	Societal	1 year	Trial/CUA
		(2) MNT group		x	x				Behavior specific/ Ind. Couns.	x			x		x				
		(3) MNT-plus-therapeutic meal group		x	x		x		See 1,2	x			x		x				
Walsh et al. 2015 (138)	Patients (>18 years) discharged from ICU, receiving a minimum of 48 hours of mechanical ventilation	Usual care + RA: *RA received training (e.g.dietetics) and deliver Ind. therapy in different domains *Ind.rehabilitation goals regularly evaluated *Telephone contact and families involved	x	x	x		x	2	Ind. therapy, Ind. rehabilitation goals.	x			x			Usual care	National Health Service	12 months	Trial/CUA
Walters et al. 2017 (139)	Community - dwelling adults (≥ 65 years) with mild frailty	Homehealth: *First appointment: learning about person domains (e.g. nutrition)/ identify goal. *Nest appointments: review goals/progress. *Final appointment: reinforce self-efficacy and new learned things. Advice on motivation and behaviors.	x	x	x			2	Pers./ tailored to each individual Identifying goals and strategies (incl. diet)	x		x		x		Usual treatment	Societal	6 months	Trial/CUA

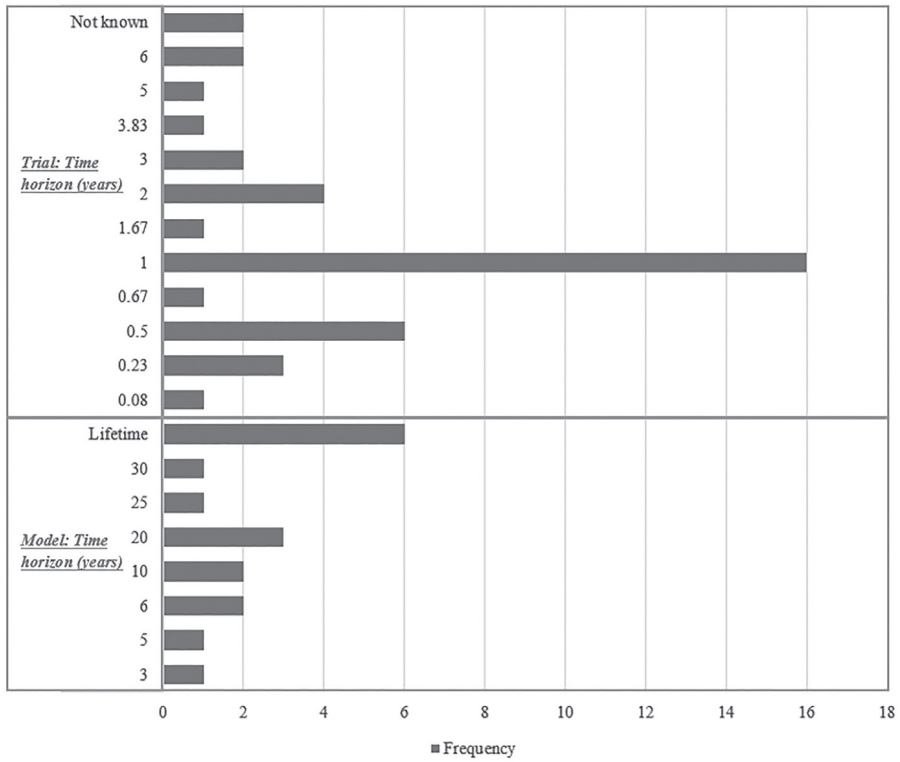
Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Whigham et al. 2015 (140)	Patients with IBS (patients with atypical symptoms or other medical, language or nutritional concerns not related to IBS were allocated to one-to one education)	FODMAP: *First consultation: define eating practices *Physiological framework *Providing literature *Positive food messages *Techniques for handling situations →was done in group education (group pathway)		x	x		x	2	Ind. Advice /counseling + dietary instructions, Clinical judgement fructose/lactose restricted.	x	x		x			One-to one education →same as intervention but then one-to-one (hypothetical arm)	-	-	Trial/CUA

Study (Author, year)	Patient population	Intervention Short description	Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms	Personalized concept/definition Short description	Psychological	Biological	Tailored	Individualized	Personalized	Other	Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
Malnourished																			
Lorefält et al. 2011 (132)	Older people living in municipal residential homes	Multifaceted intervention design: nutritional care including theoretical/practical issues. * Well-nourished: Snacks between meals. * Malnourished: Appetizer at lunch and extra individual snacks.		x	x			2	Ind. Meals, Snacks distributed by individual needs/preferences	x			x			Staff education on MNA and residents usual meal routines	-	1 year	Trial/CCA
Milte et al. 2016 (165)	Fall-related hip fracture (>70 years), no severe cognitive impairment, BMI of 18.5-35 kg/m2	Individual nutrition therapy and exercise regime.	x	x	x			2	Ind. Couns. /care plan	x			x			Usual rehabilitation programs	Healthcare	6 months	Trial/CUA

Study (Author, year)	Patient population	Intervention Short description							Personalized concept/definition Short description							Comparator	Perspective	Time horizon	Design (trial/model;-CEA/CUA/CBA/CCA)
			Exercise	Nutrition	Face to face	Computer-based	Telephone	Study arms		Psychological	Biological	Tailored	Individualized	Personalized	Other				
van der Pols-Vijlbrief et al. 2017 (133)	Community - dwelling older adults (>65 years) receiving home care with or at risk of undernutrition	Pers. action plan: (a) Personal cause-specific tips for own use (b) Referring to neighborhood initiatives (c) Advising participants to approach healthcare professionals Follow-up via phone to evaluate/motivate.		x	x		x	2	Pers. action plan (underlying causes, personal needs, preferences)	x				x		Usual care	Societal	6 months	Trial/CEA/CUA
Sharma et al. 2018 (166)	Hospitalized patients (≥60 years) who were confirmed as malnourished	Extended nutritional intervention: with nutrition intervention of oral supplements, mid-meal snacks and food fortification considering individual preferences, medical conditions, protein-, vitamin-, energy- and mineral requirements and post-discharge follow-up care.		x	x		x	2	Individual l (underlying medical conditions, intake, preferences)	x	x		x			Usual care	Australian (Medicare) healthcare	3 months	Trial/CEA/CUA
Wyers et al. 2013 (141)	Patients (≥55 years) admitted for surgical treatment of hip fracture	Intensive nutritional intervention comprising regular dietetic counseling and oral nutritional supplementation.		x	x		x	2	Ind. Tailored advice	x		x	x			Usual care	Societal	6 months	Trial/CEA/CUA

BMI, Body Mass Index; C, Comparator; CBA, Cost benefit analysis; CCA, Cost consequence analysis; CEA, Cost Effectiveness Analysis; CHD, Coronary heart disease; Couns., Counseling; CUA, Cost Utility Analysis; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; FPG, fasting plasma glucose; GP, general practitioner; HbA1c, Hemoglobin A1c; HMO, Health Maintenance Organization; I, Intervention; ICU, intensive care unit; IGT, Impaired glucose tolerance; Ind., Individualized; kg, kilograms; LSM, lifestyle modification; m, meters; MNA, Mini Nutritional Assessment; MNT, Medical nutrition therapy; NIDDM, Non-insulin-dependent diabetes mellitus; Pers., Personalized; RA, rehabilitation assistant.
x Study scored on this aspect.
^ Used data from DPP and DPS trials.
- No information is given in study.

Appendix 2.4: Frequencies of time horizons



Distribution of time horizons. This figure shows the variation in time horizons used in the studies, separated by design (trial/model). The y-axis shows the different time horizons found in years and the x-axis shows the frequencies. Since 4 studies used both trial and model-based data, a total of 57 (53+4) observations can be found in the figure.

Appendix 2.5: Modeling approaches of DPP and DPS studies

Study	Model type	(Intermediate) outcomes: mechanism of intervention effect	Assumed intervention effect	Utility source	Country + discount rates
DPP					
Ackermann et al. 2006(112)	Markov 4 states: IGT, diabetes, complications, death	Treatment effect is obtained from the trial: risk of diabetes is reduced. Changes in **HbA1c** and diabetes treatments were modeled to reflect those observed in the UKPDS intensive therapy arm.	**Lasting**: Reduction remained constant.	IGT who developed diabetes: from model by applying penalty scores for demographic, treatment, and disease state variables to a baseline utility score. For those developing hypertension, CHD, or CVD before developing diabetes: mean year 3 health utility score for a male DPP participant as a baseline and applied the same penalty scores as above.	UK: 3% costs and effects

Study	Model type	(Intermediate) outcomes: mechanism of intervention effect	Assumed intervention effect	Utility source	Country + discount rates
Eddy et al. 2005(114)	Archimedes model: full scale simulation model of human physiology, diseases, behaviors, interventions and health-care systems; includes all biological variables and outcomes related to diabetes and complications. The model simulates what happens in the clinical states, between the annual jumps and inside the transition probabilities.	I reduced **weight, blood pressure and FPG levels and improves LDL cholesterol, HDL cholesterol and total cholesterol**. Metformin reduces **FPG and 2-hour oral glucose tolerance, decrease LDL cholesterol and triglyceride levels and retard weight gain.**	**Waning:** After an initial weight loss of about 7%, the simulated persons' weight loss gradually decreased to 4% after 3 years as seen in DPP, and that degree of weight loss persisted as long as they received the I. The Archimedes model shows the same phenomenon of a diminishing relative effect as Herman et al. 2005(116), but with greater accuracy because it incorporates the fact that neither the transition rate nor the relative effect of lifestyle is constant.	People without diabetes: from the DPP study. Diabetes and its complications: Coffey et al.(184)	3% costs and QALYs

Study	Model type	(Intermediate) outcomes: mechanism of intervention effect	Assumed intervention effect	Utility source	Country + discount rates
Herman et al. 2005(116)	Markov 5 states: IGT, onset of diabetes, clinically diagnosed diabetes, diabetes with complications, death.	Blood pressure and lipid levels progressed as they did in DPP participants and cardiovascular complications occurred as they would in type 2 diabetes according to risk factors and HbA1c level.	**Waning:** Lifestyle and metformin I would be applied until diabetes onset and health and Quality of life benefits associated with the I persisted until diabetes onset. Penalties were applied after the 3-year period for utilities in the IGT state associated with hypertension and CVD risk factors and in diabetes state based upon treatments, CVD risk factors and complications.	UKPDS	US: 3% costs and effects
Smith et al. 2016(153)	Markov 4 states: Nondiabetic, stable diabetes, diabetes with complications, and death.	Diabetes incidence was a function of baseline **BMI and weight change**, with odds ratios for diabetes risk based on weight change derived from a nationally representative sample of US adults adjusted for age, baseline BMI, sex, race education, systolic blood pressure, skin hold ratio and reported change in physical activity.	Not appointed	No diabetes: Smith et al. 2010(185) Stable diabetes: Smith et al. 2010(185) Herman et al. 2005(116)	US: 3% costs and effects

Study	Model type	(Intermediate) outcomes: mechanism of intervention effect	Assumed intervention effect	Utility source	Country + discount rates
DPS					
Avenell et al. 2004(119)	Markov 3 states: IGT, diabetes, death.	Treatment effect is taken from the trial: risk of diabetes is reduced (**not considered the impact of I on hypertension, hypercholesterolemia and CVD.**	Not appointed	Diabetes: from the Cost Utility Analysis database of Harvard University. IGT: from Clegg et al.2002(186)	UK: 6% costs and 1.5% QALYs
From Dalziel et al.(158): *Eriksson et al. 1999*(127)	Markov 4 states: NGT, IGT, diabetes, death	Treatment effect is taken from the trial: risk of diabetes is reduced. Not described in much detail: **model parameters were informed by the intermediate outcome measures reported in the seminal studies and other pertinent data sources**. Lifetables are adjusted for metabolic status and weight.	**Lasting**: Length of benefit is extended to 20 years due to a maintenance of outcomes for the last few years of trial data, indicating that continuation of effect is likely.	Colagiuri et al. 2003 (187)	Australia: 5% costs and effects
Galani et al. 2007(109)	Markov 7 states: Overweight/ obese, hypertension, diabetes, hypercholesterolemia, coronary heart disease, stroke, death.	Reduction in **BMI,** and **CVD** risk factors **(systolic blood pressure, total cholesterol,** and **HDL cholesterol).**	**Waning**: Effect of I on CVD risk factors and weight loss is maintained up to six years, thereafter subjects start to regain weight linearly for a period of 4 years i.e. after ten years weight loss went back to the initial weight. *Assumption is sustained by the extended follow-up of the trial.*	Utilities for overweight and obese people: Macran 2004 (188) Utilities changes due to decreases in BMI: Hakim et al. 2002.(189) Utilities associated with the complications of obesity: Jia et al. 2005.(190)	Switzerland: 3% costs and effects

Study	Model type	(Intermediate) outcomes: mechanism of intervention effect	Assumed intervention effect	Utility source	Country + discount rates
Lindgren et al. 2007(118)	Markov 7 states: IGT, Diabetes, MI (2 states), stroke (2 states), death.	Relative risk reduction of developing diabetes. **CVD** risk factors (**total cholesterol** (decreasing), **HDL** (increasing), **HBA1c** (decreasing), **Systolic blood pressure** (decreasing)	**Not lasting:** No effect of I was assumed once treatment was discontinued.	UKPDS trial by Clarke et al. 2002. (191)	Sweden: 3% costs and effects

BMI, Body Mass Index; DPP, diabetes prevention program; DPS, diabetes prevention study; CHD, coronary heart disease; CVD, Cardiovascular Disease; FPG, fasting plasma glucose; HDL, high density lipoprotein; I, intervention; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MI, myocardial infarction; NGT, Normal Glucose Tolerance; UKPDS, UK Prospective Diabetes Study; QALY, Quality-Adjusted Life Year.

Appendix 2.6: Economic outcomes

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Obesity/Diabetes/IGT population: DPP intervention					
Ackermann et al. 2006(112)	(a) DPP begun at age 50: $758 (b) DPP delayed until age 65+: $231	(a) 0.59 QALYs (b) 0.27 QALYs	(a) $1,288 per QALY (b) $1,575 per QALY	No conclusion	*Tend to be CE,* more CE <65 years.
Caro et al. 2004(113)^	(1) Lifestyle vs no treatment: $233 (2) Lifestyle vs metformin: $1,232 (3) Lifestyle vs acarbose: $1,130	(1) +0.31 survival years (2) +0.17 survival years (3) +0.11 survival years	(1) $749 per LYG (2) $7,252 per LYG (3) $9,988 per LYG	Yes	-
Eddy et al. 2005(114)	Soc. persp. (I vs C (see table 2.1)): (1) DPP lifestyle: $6,903 (2) Lifestyle when FPG level >125 mg/d: $3,066	Soc. persp. (I vs C): (1) 0.034 QALYs (2) 0.125 QALYs	Health plan persp. (I (1) vs no prev. prog.): $143,000 per QALY Soc. persp.: (1) $201,818 per QALY (2) $24,523 per QALY	No conclusion	Tend towards not CE. *Delaying the intervention till patients get diabetes (2) is more CE.*
Herman et al. 2005(116)	Health system persp.: (1) Lifestyle vs placebo: $635 (2) Lifestyle vs metformin: $-3,287 Soc. persp.: (1) $4,967 (2) $1,219*	Both perspectives: (1) 0.57 QALYs (2) 0.45 QALYs	Health system persp.: (1) $1,100 per QALY (2) Dominant Soc. persp.: (1) $8,790 per QALY (2) $2,709 per QALY*	Yes	-
Icks et al. 2007(131)	(2) Lifestyle vs no I: Statutory health insurance persp.: €856,507 Soc.persp. : €4,961,340	(2) prevent or delay 184 cases	Statutory health insurance persp.: €4,664 per case prevented Soc. Persp.: €27,015 per case prevented	No	Total cost and cost per case of diabetes avoided was high.

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Palmer et al. 2004(108)	Costs: (a) Australia: (2) Lifestyle vs C: €–636 (3) Lifestyle vs metformin: €–592 (b) France: (2) €–455; (3) €–211 (c) Germany: (2) €–584; (3) €–319 (d) Switzerland: (2) €–1,036; (3) €–481 (e) UK: (2) €1,021; (3) €643	LYG: (a) (2) 0.08; (3) 0.04 (b) (2) 0.07; (3) 0.04 (c) (2) 0.07; (3) 0.04 (d) (2) 0.06; (3) 0.03 (e) (2)0.16; (3) 0.07	Cost/LYG (a) dominant (b) dominant (c) dominant (d) dominant (e) (2)€ 6,381; (3) €7,144	Yes	-
Ramachandran et al. 2007(115)	(1) LSM vs C: 7,397 INR (2) LSM + metformin vs C: 9,405 INR	# individuals needed to treat for a prevented case of diabetes(NNT):(1)6.4 (2)6.5	Cost/NNT (INR): (1) 47,341 (2) 61,133	Yes	-
Smith et al. 2016(153)	Healthcare persp.: $591 Soc. persp.: $1,209	0.0412 QALYs	Healthcare: $14,351 per QALY Soc. persp.: $29,331 per QALY	Yes	-
The Diabetes prevention program 2003(104)	Healthcare persp.: (1) Lifestyle vs placebo: $2,269 (2) Lifestyle vs metformin: $78 Soc. persp.: (1) $3,540; (2) $1,128	(1) 0.072 QALYs (2) 0.050 QALYs	Healthcare: (1) $15,700 per prevented case of diabetes/ $31,500 per QALY Soc. persp.: (1) $24,400 per prevented case of diabetes/ $51,600 per QALY	Yes	-
Obesity/Diabetes/IGT population: DPS intervention					
Avenell et al. 2004(119)	6 years: £485	6 years: 0.036 QALYs	6 years: £13,389 per QALY 15 years: £5,825 per QALY	No conclusion	Declining ICER over time. *CE later in time.*

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
From Dalziel et al.(158): Eriksson et al. 1999(127) Follow-up	807 AU$	Weight loss(kg): I=3.5;C=0.8 Incidence of diabetes: I=20.0%; C=42.6%	300 AU$ per kg lost 9,500 AU$ per diabetes case prevented	No conclusion	-
Extrapolated (127,158)	769 AU$	0.41 QALYs	1,880 AU$ per QALY	Yes	-
Galani et al. 2007(109)	(a) Overweight: Male (M):384 CHF/ Female (F):490 CHF (b) Borderline: M:-99 CHF/ F:16 CHF (c)Moderately obese:M:44 CHF/F:145 CHF	LY: all subgroups: 0.01 QALY: (a) M: 0.25/F: 0.23 (b) M: 0.28/F: 0.25 (c) M: 0.29/F: 0.26	Cost per LY (CHF): Borderline: M:-11,200 (dominant)/F:1,700 Cost per QALY: Borderline: M:-354 (dominant)/ F: 64	Yes	-
Lindgren et al. 2007(118)	€468	0.20 QALYs	€2,363 per QALY	Yes	-
Obesity/Diabetes/IGT population: other interventions					
Barton et al. 2009(125)	(1) See table 2.1 for I: £646.71 (2) See table 2.1 for I: £766.64	(1) 0.062 QALYs (2) 0.048 QALYs	(1) £10,649 per QALY (2) Dominated by 1	Yes	Lot of uncertainty
Befort et al. 2010(142)	(1) Program costs group (I) vs individual (C):+ $-178.53 (2) Participant costs (I) vs (C):+ $106.95	1,8 kg+	(1;I) $ 328.60; (1+2;I) $714.43 ‡ (1;C) $764.52; (1+2;C) $1,029.06 ‡ *No real incremental costs/effect/ ICER*	No	Group session is more CE than individual treatment.
From Dalziel et al.(158): Swinburn et al. 2001(159) Follow-up	241 AU$	Mean weight loss(kg): I=-1.06; C=-0.26; BMI: I-0.72; C=0.59	Control group dominates at 5 years	No conclusion	-

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Extrapolated (158,159)	241 AU$	0.024 QALYs	10,000 AU$	Yes	-
From Dalziel et al.(158): Pritchard et al. 1999(160)	88 AU$	Mean weight loss (kg): I=-6.13; C=0.58	13 AU$ per additional kilogram lost	No conclusion	-
Franz et al. 1995(144)	I vs C (per patient costs): $70+ Without HbA1c: (I) (per patient cost) $95.07	Mean change in (fPGL): (I) -1.1 +/- 2.8 mmol/L (C) -0.4 +/- 2.7 mmol/L Mean change in HbA1c assay (% point): (I) -0.93 +/- 1.63 mmol/L (C) -0.69 +/- 1.67 mmol/L	Each unit of change in fPGL can be achieved with an investment of $5.75 by (C) or of $5.84 by implementing (I). If net costs are considered (per patient costs-cost savings due to therapy changes), the CE ratios become (C) $5.32; (I) $4.20. *No real incremental costs/ effect/ICER.*	Yes	-
Glasgow et al. 1997(145)	Cost per patient (not incremental): $115-139.	-	$7–$8 per mg/dl ↓ cholesterol $52-$63 per 1% ↓ fat intake	Yes	-
Goldfield et al. 2001(146)	Cost per family (I) mixed: $1,390.72 Cost per family (C) group: $491.48	-	I:% overweight ↓ units per 1$; 0.005 C:% overweight ↓ units per 1$: 0.014 I:Z-BMI↓units achieved per 1$:0.0004 C:Z-BMI↓units achieved per 1$: 0.001	No	Group more CE than mixed.
Kaplan et al. 1987(105)	Diet exercise vs C: $1000 per participant	0.092 well-years	$10,870 per well-year	No conclusion	Benefits/cost comparable to alternatives. *Tend to be CE.*
McConnon et al. 2007(106)	Excluding fixed costs: £-55.04 Total costs: £716.28	0.02 QALYs	£39,248 per QALY	No	-

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Olsen et al. 2005(111)	In 2001 DKK: (a) Without IHD: Total: 1,325; Dietitian:1,642; GP: 751 (b) With IHD: Total: 1,293, Dietitian:1,642, GP: 755	LYG: (a) Total:0.1023; Dietitian: 0.0700; GP: 0.1608 (b) Total: 0.0528; Dietitian: 0.0274; GP: 0.0919	DKK/year: (a) Total: 12,962; Dietitian: 23,469; GP:4,670 (b) Total: 24,481; Dietitian: 59,987; GP:8,213	Yes	-
Redman et al. 2017(151)	Intervention costs: (1)In-person: US$ 347; (2)Phone: US$ 97 Clinic costs: (1) US $419; (2) US $215	Less exceeded the IOM 2009 GWG guidelines in both interventions ((1) 56%; (2) 58%) compared to C 85%). Overall I adherence greater in (2) than (1) (76.5% vs 60.8%)	No real values for CE are given. *No real incremental cost/effects/ ICER.*	Yes	-
Segal et al. 1998(110)	-	Intensive diet vs control: (1) LYG:Mixed 155; IGT 213 (1) Diabetes years↓:Mixed 144; IGT 259	Cost per LYG (Net cost): IGT only: net saving Mixed: AU$2,600	Yes	-
Sherwood et al. 2006(107)	(1) Mail: $50.45 (2) Phone: $127.39 (C): $42.18	Weight change (kg): (1) -0.70; (2) -0.96; (C) -0.59	(1 & C) $72 per 1 kg weight loss (2) $132 in producing 1 kg weight loss *No real incremental cost/effects/ ICER.*	No conclusion	-
Toobert et al. 2007(155)	Total costs I vs C: $409,165 or $2,510 per MLP participant ($309,302 direct costs).	-	$221 per unit improvement in calories; $1,434 per kilocalorie ↑ in physical activity; $1,168 per unit ↑ in stress management.	No conclusion	Cost are relatively high compared to other estimates. *Tend to be not CE.*
Wylie-Rosett et al. 2001(157)	(1) Workbook+comp.: $41.99 pp (2) Workbook+comp.+ staff: $133.74 pp	Pounds lost: (1) 4.7; (2) 7.4	Mean cost per pound lost: (1) 6.23; (2)18.78	No conclusion	Costs were modest in all arms. Satisfaction ↑ as I intensity ↑.*Tend to be CE*

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
General/Healthy population					
From Dalziel et al.(158): de Lorgeril et al. 1999(150) Follow-up	287 AU$ pp	Non-fatal MI averted:8.6/100 Deaths averted: 5.4/100	AU$ 3,300 per non-fatal MI averted AU$ 5,300 per death averted	No conclusion	-
Extrapolated (150,158)	787 AU$	0.77 QALYs	1,020 AU$	Yes	-
From Dalziel et al.(158) Steptoe et al. 2003(137) Follow-up	1,203 AU$	↑ in % of eating more than 5 serves of fruit and vegetables per day; I= 42.2; C= 26.8	AU$ 5,800 per % point ↑	No conclusion	-
Extrapolated (137,158)	917 AU$	0.087 QALYs	10,600 AU$	Yes	-
Leigh et al. 1992(149)	Total direct and indirect costs: I ↓ 11% (-$178)⁺ C ↑ 6,3% ($111)⁺	Health risk scores: I ↓ 4.3%. C ↑ 7,2%	Benefit-cost ratio: $1 expended on the program, roughly $5 was saved in direct costs	No conclusion	Stated that it is a low-cost I and effective. *Tend to be CE.*

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Lindgren et al. 2003(117)	(1) Dietary advice vs no intervention: (a) Declining effect of I (SEK): Soc. persp.: 2,892 Payer persp.: 2,247 (b) Remaining effect I (SEK): Soc. persp.: 14,106 Payer persp.: 1,164 (2) Combination+ (a) Declining effect of I (SEK): Soc. persp.: 3,222 Payer persp.: 2,478 (b) Remaining effect I (SEK): Soc. persp.: 9,700 Payer persp.: 1,840	(1a) 0.0228 LYG (1b) 0.0997 LYG (2a) 0.016 LYG+ (2b) 0.063 LYG+ (1a) 0.022 QALYs (1b) 0.086 QALYs (2a) 0.016 QALYs (2b) 0.055 QALYs	SEK/LYG: (1a) Soc. persp.: 127,065/ Payer.: 98,725 (1b) Soc. persp.: 141,555/ Payer.: 11,642 (2a) Soc. persp.: 201,375/ Payer: 154,875 + (2b) Soc. persp.: 153,968/ Payer: 29,206 + SEK/QALY: (1a) Soc. persp.: 130,505/ Payer. 101,398 (1b) Soc. persp.: 164,348/ Payer.: 13,561 (2a) Soc. persp.: 201,375/ Payer: 154,875 + (2b) Soc. persp.: 176,363/ Payer: 33,455 +	Yes	(1) Dietary advice appears to be the most CE independent of the study perspective.
Schulz et al. 2014(135)	(1) Sequential vs C: €183.76 (2) Simultaneous vs C: €868.00 (3) Sequential vs simultaneous: €-684.24	(1) LFS 0.04; QALYs -0.01 (2) LFS 0.08; QALYs -0.03 (3) LFS -0.04; QALYs 0.02	(1) €4,594 per LFS; QALY dominated (2) €10,850 per LFS; QALY dominated (3) €17,106 per LFS; QALY dominant	Sometimes	CE in case of LFS
Sukhanova et al. 2009(154)	(1) Tailored: $81 pp (2) HOBI: $184 pp (C) Untailored: $69 pp	F&V consumption: (1) +2.68 ;(2) +2.80 (C) +2.34	$ per extra serving in F&V consumption: (1) $27 ;(2) $61 (C): $35	Yes	-
Other population					
Broekhuizen et al. 2015(126)	€-237	LDL-C: -0.14 QALYs: -0.002	€1,729 per 1 mmol/l LDL cholesterol; €145,899 per QALY	No	-

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Chatterton 2018(164)	Healthcare persp.: $-856 Soc. Persp. $-2,591	0.026 QALYs (after imputation, unadjusted)	Dominant (68% and 69% probability that dietary support is dominant)	Yes	-
Emmons et al. 2005(143)	$45.53	Difference in proportions that dropped at least 1 risk factor: 0.12	$379 per risk factor dropped (only considering I benefit/no regression) $228 per unit change (considering regression + progression of risk factors)	Yes	-
Ethgen et al. 2016(128)	(1)1 portion/day: €-255 – €421 (2)2 portions/day: €88 – €798 (3)3 portions/day: €407–€1,174	(1) 0.004-0.018 QALYs (2) 0.006 to 0.026 QALYs (3) 0.009-0.028 QALYs	(1) €-12,237 – €94,304 per QALY (2) €3,390 – €123,122 per QALY (3) €14,602 – €136,244 per QALY	Sometimes	CE when lower than €45,000 per QALY
Gillespie et al. 2017(129)	(a) Northern Ireland: €-2,914 (b) Republic of Ireland: €-126 (c) Combined: €-1,092	(a) 0.105 QALYs (b) -0.034 QALYs (c) 0.009 QALYs	Probability of I being CE: (a) 1.000 for each of the threshold. (b) Threshold per QALY/probability: €5,000/0.434; €15,000/0.232; €20,000/0.180; €25,000/0.150; €35,000/0.115 and €45,000/0.098 (c) Threshold per QALY/probability: €5,000/0.986; €15,000/0.965; €20,000/0.960; €25,000/0.948; €35,000/0.925; €45,000/0.905	Sometimes	Intervention is CE in (a) Northern Ireland and (c), but not in the (b)Republic of Ireland.
Herman et al. 2014(147)	Direct costs: $302; Soc. costs: $-1,138 Lost productivity costs: $-1,440 Employer costs: $-1,187	CVD event risk: -3.3% CVD mortality risk: -0.9% QALYs: 0.01	Only a scatterplot is given.	Yes	-
Holt et al. 2018(130)	(1) Health-care cost: £870 (2) Soc. cost: £1,295	(a) EQ-5D: 0.0035 QALYs (b) SF-6D: 0.0148 QALYs	Pound per QALY: (1a) 246,921; (2a) 67,543 (1b) 58,688; (2b) 87,358	No	-

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Price et al. 2006(134)	Costs I £21,29 pp; Costs C: £23,10 pp	Overall: acceptable range by 12 of (/)13(92%) participants. Snack type acceptable: 11/14 (79%). Snack easy to eat:12/14(86%) Enjoying them:13/14(93%)	-	Yes	-
Sikand et al. 2000(152)	Net savings due to ↓ antihyperlipidemic medication: $29,549.10 or $687.19 pp	↓: total cholesterol 11%, low-density lipoprotein cholesterol 9%, triglycerides 22%, BMI 2%. ↑: high density lipoprotein cholesterol 4%.	CBR shows that for each dollar spent on MNT, $3.58 was averted in statin therapy	Yes	-
Speed et al. 2010(136)	(1) Personalized arm vs C: £-13.34	(1) 0.02 QALYs	-	No conclusion	No ICER due to low # patients. *Tend to be CE*
Troyer et al. 2010(156)	(1) Meals only: $2,619 (2) MNT only: $72 (3) Meals + MNT: $3,470	(1) 0.0298 QALYs (2) 0.0150 QALYs (3) 0.0208 QALYs	(1) $87,825 per QALY (2) $4,807 per QALY (3) $166,980 per QALY	Sometimes	(1) and (2) CE, (3) not CE.
Walsh et al. 2015(138)	+$3000	No benefit/lose	Dominated	No	But satisfaction ↑
Walters et al. 2017(139)	I: £307 pp. Lower NHS costs and care support costs in I, but a large variability and may be a chance finding.	CALYs higher in I than C: 0.017. No sig. difference in QALYs.	-	No conclusion	No ICER (small sample size + high variability in costs). Potential to be CE
Whigham et al. 2015(140)	I vs C total costs: £-12,418.02 *Costs per group unknown.*	(I) Group: 0.0295 QALYs (C) 1-to-1: 0.0261 QALYs	(I) Group: £3,052.36 per QALY *This is not calculated for the C arm*	No conclusion	*Group I tend to be CE*
Malnourished					
Lorefält et al. 2011(132)	I: €1,005; C: €921 *No real incremental costs*	Bodyweight (↑ is better): I: +2.7 kg; C: -0.6	-	No conclusion	Individualized meals(I):↑ body weight + nutritional status without ↑ meal costs. *Tend to be CE.*

Study	Incremental Costs †	Incremental Effects	ICER/ICUR §	Authors' conclusions	
				Cost-effective?	Additional remarks: ¶
Milte et al. 2016(165)	567 AU$	0.02 QALYs	28,350 AU$ per QALY	Yes	High level of uncertainty
van der Pols-Vijlbrief et al. 2017(133)	-€274.00	Weight gain (kg): 0.39 0.01 QALYs	€-741 per 1 kg gain €-32,173 per QALY	Sometimes	CE for QALY as outcome, but not for weight gain. *These conclusions are based on sensitivity analysis.*
Sharma et al. 2018(166)	-$907 pp	Unit improvements in PG-SGA: 1.3238 units. 0.0050 QALYs	Dominant (although this was not reported as such by the authors)	Yes	-
Wyers et al. 2013(141)	-	1.91 kg -0.02 QALYs	€241 soc. costs per kg weight ↑ €36,943 soc. costs per QALY	Sometimes	CE for weight as outcome. Low probability CE QALYs as outcome, except in subjects aged <75 years.

AU, Australia; BC, Basic nutrition Care; C, Comparator; CALY, capability-adjusted life-years; CBR: Cost Benefit Ratio; CE, Cost-effective; Comp., computer; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; F, Female; F&V, Fruit & Vegetable; fPGL, fasting plasma glucose level; GP, general practitioner; GWG, gestational weight gain; HbA1c, Hemoglobin A1c; HOBI, human online behavioral interaction; I, Intervention; ICER, Incremental cost-effectiveness ratio; ICUR, Incremental cost-utility ratio; IGT, Impaired glucose tolerance; IHD, Ischemic Heart Disease; kg, kilograms; LDL-C, Low-density lipoprotein ; LFS, lifestyle factor score; LSM, lifestyle modification; LY, Life Years; LYG, Life Years Gained; M, Male; MI, myocardial infarction; MLP, Mediterranean Lifestyle Program; MNT, Medical nutrition therapy; NNT, Number of individuals needed to treat; Persp., Perspective; PG-SGA, Patient generated subjective global assessment; PGC, Practice Guidelines nutrition Care; Pp, per person; QALY, Quality-Adjusted Life Years; Soc., Societal; UK, United Kingdom.
† All study arms are shown by 1,2,3 in the table. a,b,c stands for the different subgroups analyzed.
§ When outcome is per QALY, meaning per QALY gained.
¶ Cursive: own interpretation.
^ Used data from DPP and DPS trial.
- No information is given in study.
* Calculated in sensitivity analysis. Cost are higher for lifestyle compared to metformin. ICUR is not calculated of lifestyle vs metformin in societal perspective, but we calculated the ICUR.
+ Calculated ourselves (no incremental values given).
# Number of.
± Cost-effectiveness calculated as per participant cost divided by intent-to-treat success rate of 10% weight loss (62% in group condition and 50% in individual condition)
↑ Increase, higher, improve. ↓ Decrease, lower

Appendix 2.7: Table of costs, effects, and cost-effectiveness

Study	*Costs/effects intervention/ perspective*	*Year costs*	*Currency article*	*Costs in article*	*QALYs*	*ICUR in article*	*ICER in article*	*CPI (2019)*	*CPI (year cost article)*	*PPP*	*Cost (2019 USD)*	*ICUR 2019 USD*	*ICER 2019 USD*
Obesity/Diabetes/IGT population: DPP intervention													
Ackermann et al. 2006(112)	(a)DPP begun at age 50	2000	USD	758	0.5885	1,288	x	107.9	72.7	1	1,125	1,911	x
	(b)DPP delayed until age 65+	2000	USD	231	0.1467+	1,575	x	107.9	72.7	1	343	2,336	x
Caro et al. 2004(113)	(1)Lifestyle vs no treatment	2000	CAD	233	x	x	749	107	75.4	1.203	276	x	887
	(2)Lifestyle vs metformin	2000	CAD	1,232	x	x	7,252	107	75.4	1.203	1,459	x	8,590
	(3)Lifestyle vs acarbose	2000	CAD	1,130	x	x	9,988	107	75.4	1.203	1,338	x	11,831
Eddy et al. 2005(114)	Health plan's persp. ((1) DPP lifestyle)	2000	USD	missing	missing	143,000	x	107.9	72.7	1	missing	212, 159	x
	Soc. Persp. ((1) DPP lifestyle)	2000	USD	6,903	0.0342	201,818	x	107.9	72.7	1	10,242	299, 424	x
	Soc. Persp. ((2) lifestyle FPG level>125)	2000	USD	3,066	0.1250	24,523	x	107.9	72.7	1	4,549	36, 383	x
Herman et al. 2005(116)	Health system persp. ((1) lifestyle placebo)	2000	USD	635	0.5773	1,100	x	107.9	72.7	1	942	1,632	x
	Health system persp. ((2) lifestyle metformin)	2000	USD	-3,287	0.45	Domi-nant	x	107.9	72.7	1	-4,877	-10, 837#	x
	Soc. Persp. ((1) lifestyle placebo)	2000	USD	4,967	0.5651	8,790	x	107.9	72.7	1	7,369	13, 041	x
	Soc. Persp. ((2)lifestyle metformin)	2000	USD	1,219	0.4500	2,709	x	107.9	72.7	1	1,809	4,019	x
Icks et al. 2007(131)	Statutory health insurance persp.	2004	EUR	856, 507	x	x	4,664	105	84.9	0.742	1,432, 197	x	7,799
	Soc. Persp.	2004	EUR	4,961, 340	x	x	27,015	105	84.9	0.742	8,296, 041	x	45,173

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Palmer et al. 2004(108)	(a)(2)lifestyle vs C	2002	EUR	-636	x	x	dominant	105.0*	77.8*	0.692*	-1,240	x	dominant
	(a)(3)lifestyle vs metformin	2002	EUR	-592	x	x	dominant	105.0*	77.8*	0.692*	-1,154	x	dominant
	(b)(2)lifestyle vs C	2002	EUR	-455	x	x	dominant	105.0*	77.8*	0.692*	-887	x	dominant
	(b)(3)lifestyle vs metformin	2002	EUR	-211	x	x	dominant	105.0*	77.8*	0.692*	-411	x	dominant
	(c)(2)lifestyle vs C	2002	EUR	-584	x	x	dominant	105.0*	77.8*	0.692*	-1,139	x	dominant
	(c)(3)lifestyle vs metformin	2002	EUR	-319	x	x	dominant	105.0*	77.8*	0.692*	-622	x	dominant
	(d)(2)lifestyle vs C	2002	EUR	-1,036	x	x	dominant	105.0*	77.8*	0.692*	-2,020	x	dominant
	(d)(3)lifestyle vs metformin	2002	EUR	-481	x	x	dominant	105.0*	77.8*	0.692*	-938	x	dominant
	(e)(2)lifestyle vs C	2002	EUR	1,021	x	x	6,381	105.0*	77.8*	0.692*	1,991	x	12,444
	(e)(3)lifestyle vs metformin	2002	EUR	643	x	x	7,144	105.0*	77.8*	0.692*	1,254	x	13,931
Ramachandran et al. 2007(115)	(1)LSM vs C	2006	INR	7,397	x	x	47,341	121	47	18.381	1,039	x	6,653
	(2)LSM + metformin vs C	2006	INR	9,405	x	x	61,133	121	47	18.381	1,322	x	8,591
Smith et al. 2016(153)	Healthcare persp.	2010	USD	591	0.0412	14,351	x	107.9	92	1	693	16, 825	x
	Soc. Persp.	2010	USD	1,209	0.0412	29,331	x	107.9	92	1	1,417	34, 387	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
The Diabetes prevention program 2003(104)	Healthcare persp. ((1) lifestyle vs placebo)	2000	USD	2,269	0.0720	31,500	15,700	107.9	72.7	1	3,366	46, 734	23,293
	Healthcare persp. ((2) lifestyle vs metformin)	2000	USD	78	0.0500	missing	x	107.9	72.7	1	116	2,314	x
	Soc. Persp. ((1) lifestyle vs placebo)	2000	USD	3,540	0.0686	51,600	24,400	107.9	72.7	1	5,252	76, 555	36,201
	Soc. Persp. ((2) lifestyle vs metformin)	2000	USD	1,128	0.0500	missing	x	107.9	72.7	1	1,674	33, 471	x
Obesity/Diabetes/IGT population: DPS intervention													
Avenell et al. 2014(119)	6 year time horizon	2001	GBP	485	0.0362	13,389	x	108	74.6	0.689	1,017	28, 095	x
	15 year time horizon	2001	GBP	missing	missing	5,825	x	108	74.6	0.689	missing	12, 215	x
From Dalziel et al.(158) Eriksson et al. 1999(127)	*Kg lost*	2006^	AUD	807	x	x	300	107	79.8	1.472	735	x	273
	Diabetes case prevented	2006^	AUD	807	x	x	9,500	107	79.8	1.472	735	x	8,648
	Extrapolated	2006^	AUD	769	0.4090	1,880	x	107	79.8	1.472	700	1,711	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Galani et al. 2007(109)	(a)Overweight M	2006	CHF	384	0.2500	missing	x	101	98.5	1.155	342	1, 368#	x
	(a)Overweight F	2006	CHF	490	0.2300	missing	x	101	98.5	1.155	437	1, 898#	x
	(b)Borderline M LY	2006	CHF	-99	x	x	-11,200	101	98.5	1.155	-88	x	-9,978
	(b)Borderline F LY	2006	CHF	16	x	x	1,700	101	98.5	1.155	14	x	1,515
	(b)Borderline M QALY	2006	CHF	-99	0.2797	-354	x	101	98.5	1.155	-88	-315	x
	(b)Borderline F QALY	2006	CHF	16	0.2500	64	x	101	98.5	1.155	14	57	x
	(c)Moderately obese M	2006	CHF	44	0.2900	missing	x	101	98.5	1.155	39	135#	x
	(c)Moderately obese F	2006	CHF	145	0.2600	missing	x	101	98.5	1.155	129	497#	x
Lindgren et al. 2007(118)	*QALYs*	2003	EUR	468	0.1981	2,363	x	105.0*	79.6*	0.692*	892	4,504	x
Obesity/Diabetes/IGT population: other interventions													
Barton et al. 2009(125)	(1) I	2006	GBP	647	0.0607	10,649	x	108	81.4	0.689	1,243	20, 465	x
	(2) I	2006	GBP	767	0.0480	Dominated by 1	x	108	81.4	0.689	1,473	30, 694	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Befort et al. 2010(142)	(1)Program group (I) vs individual (C)	2010	USD	-179	x	x	x	107.9	92	1	-209	x	x
	(2)Participant group (I) vs individual (C)	2010	USD	107	x	x	x	107.9	92	1	125	x	x
	(1) I	2010	USD	x	x	x	328	107.9	92	1	x	x	385
	(1+2) I	2010	USD	x	x	x	714	107.9	92	1	x	x	838
	(1) C	2010	USD	x	x	x	765	107.9	92	1	x	x	896
	(1+2) C	2010	USD	x	x	x	1,029	107.9	92	1	x	x	1,206
From Dalziel et al.(158) Swinburn et al. 2001(159)	Weight loss	2006^	AUD	241	x	x	Cdominates at 5 years	107	79.8	1.472	219		Cdominates at 5 years
	Extrapolated	2006^	AUD	241	0.0241	10,000	x	107	79.8	1.472	219	9,103	x
From Dalziel et al.(158) Pritchard et al. 1999(160)	Weight loss	2006^	AUD	88	x	x	13	107	79.8	1.472	80	x	12
Franz et al. 1995(144)	I vs C	1993	USD	70	x	x	x	107.9	60.9	1	124	x	x
	I vs C without HbA1c	1993	USD	95	x	x	x	107.9	60.9	1	168	x	x
	Change in fPGL C	1993	USD	x	x	x	6	107.9	60.9	1	x	x	10
	Change in fPGL I	1993	USD	x	x	x	6	107.9	60.9	1	x	x	10
	CE ratio C	1993	USD	x	x	x	5	107.9	60.9	1	x	x	9
	CE ratio I	1993	USD	x	x	x	4	107.9	60.9	1	x	x	7

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Glasgow et al. 1997(145)	Cholesterol lowest value range	1997	USD	115	x	x	7	107.9	67.7	1	183	x	11
	Cholesterol highest value range	1997	USD	139	x	x	8	107.9	67.7	1	221	x	13
	Fat intake lowest value range	1997	USD	115	x	x	52	107.9	67.7	1	183	x	83
	Fat intake highest value range	1997	USD	139	x	x	63	107.9	67.7	1	221	x	100
Goldfield et al. 2001(146)	I mixed overweight	2001	USD	1,391	x	x	1	107.9	74.7	1	2,008	x	1
	C group overweight	2001	USD	491	x	x	1	107.9	74.7	1	710	x	1
	I mixed BMI	2001	USD	1,392	x	x	1	107.9	74.7	1	2,008	x	1
	C group BMI	2001	USD	491	x	x	1	107.9	74.7	1	710	x	1
Kaplan et al. 1987(105)	Diet exercise vs C	1987	USD	1,000	x	x	10,870	107.9	47.9	1	2,252	x	24,477
McConnon et al. 2007(106)	Excluding fixed costs	2007	GBP	-55	x	x	x	108	83.3	0.689	-103	x	x
	Total costs	2007	GBP	716	0.0183	39,248	x	108	83.3	0.689	1,345	73, 706	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Olsen et al. 2005(111)	(a) Total	2001	DKK	1,325	x	x	12,962	103.0	78	7	259	x	2,537
	(a) Dietitian	2001	DKK	1,642	x	x	23,469	103.0	78	7	321	x	4,594
	(a) GP	2001	DKK	751	x	x	4,670	103.0	78	7	147	x	914
	(b) Total	2001	DKK	1,293	x	x	24,481	103.0	78	7	253	x	4,792
	(b) Dietitian	2001	DKK	1,642	x	x	59,987	103.0	78	7	321	x	11,741
	(b) GP	2001	DKK	755	x	x	8,213	103.0	78	7	148	x	1,608
Redman et al. 2017(151)	I ((1)In-person)	2017	USD	347	x	x	missing	107.9	103.4	1	362	x	missing
	I ((2)Phone)	2017	USD	97	x	x	missing	107.9	103.4	1	101	x	missing
	C ((1)In-person)	2017	USD	419	x	x	missing	107.9	103.4	1	437	x	missing
	C ((2)In-person)	2017	USD	215	x	x	missing	107.9	103.4	1	224	x	missing
Segal et al. 1998(110)	Mixed	1997	AUD	missing	x	x	2,600	107	62.1	1.472	missing	x	3,041
Sherwood et al. 2006(107)	(1)Mail	2006	USD	50	x	x	72	107.9	85.1	1	64	x	91
	(2)Phone	2006	USD	127	x	x	132	107.9	85.1	1	161	x	167
	C	2006	USD	42	x	x	x	107.9	85.1	1	53	x	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Toobert et al. 2007(155)	Total costs I vs C (calories)	2007	USD	409, 165	x	x	221	107.9	87.5	1	504,372	x	272
	Total costs I vs C (physical activity)	2007	USD	409, 166	x	x	1,434	107.9	87.5	1	504,373	x	1,768
	Total costs I vs C (stress management)	2007	USD	409, 167	x	x	1,168	107.9	87.5	1	504,374	x	1,440
	Total costs I vs C per MLP participant	2007	USD	2,510	x	x	x	107.9	87.5	1	3,094	x	x
	Direct costs	2007	USD	309, 302	x	x	x	107.9	87.5	1	381,272	x	x
Wylie-Rosett et al. 2001(157)	(1) Workbook + comp	2001	USD	42	x	x	6	107.9	74.7	1	60	x	9
	(2) Workbook + comp + staff	2001	USD	134	x	x	19	107.9	74.7	1	193	x	27
General/Healthy population													
From Dalziel et al.(158) Lorgeril et al. 1999(150)	Non-fatal MI	2006^	AUD	287	x	x	3,300	107	79.8	1.472	261	x	3,004
	Death	2006^	AUD	287	x	x	5,300	107	79.8	1.472	261	x	4,825
	Extrapolated	2006^	AUD	787	0.7716	1,020	x	107	79.8	1.472	716	928	x
From Dalziel et al.(158) Steptoe et al. 2003(137)	Fruit and vegetables intake	2006^	AUD	1,203	x	x	5,800	107	79.8	1.472	1,095	x	5,280
	Extrapolated	2006^	AUD	917	0.0865	10,600	x	107	79.8	1.472	835	9,649	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Leigh et al. 1992(149)	Total direct + indirect costs I	1992	USD	178	x	x	missing	107.9	59.2	1	324	x	missing
	Total direct + indirect costs C	1992	USD	111	x	x	missing	107.9	59.2	1	202	x	missing
	Benefit-cost ratio	1992	USD	1	x	x	missing	107.9	59.2	1	2	x	missing
	Saved in direct costs	1992	USD	5	x	x	missing	107.9	59.2	1	9	x	missing
Lindgren et al. 2003(117)	(1) Soc. (a) declining	2000	SEK	2,892	0.0222	130,505	127, 065	107	83.2	8.918	416	18, 767	18,273
	(1) Payer (a) declining	2000	SEK	2,247	0.0222	101,398	98,725	107	83.2	8.918	323	14, 582	14,197
	(1) Soc. (b) remaining	2000	SEK	14,106	0.0858	164,348	141, 555	107	83.2	8.918	2,029	23, 634	20,356
	(1) Payer (b) remaining	2000	SEK	1,164	0.0858	13,561	11,642	107	83.2	8.918	167	1,950	1,674
	(2) Soc. (a) declining	2000	SEK	3,222	0.016	201,375	201, 375	107	83.2	8.918	463	28, 959	28,959
	(2) Payer (a) declining	2000	SEK	2,478	0.016	154,875	154, 875	107	83.2	8.918	356	22, 272	22,272
	(2) Soc. (b) remaining	2000	SEK	9,700	0.055	176,363	153, 968	107	83.2	8.918	1,395	25, 362	22,141
	(2) Payer (b) remaining	2000	SEK	1,840	0.055	33,455	29,206	107	83.2	8.918	265	4,811	4,200

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Schulz et al. 2014(135)	(1) Sequential vs C	2014	EUR	184	-0.0100	Dominated	4,594	106	99.4	0.788	249	-24, 918#	6,229
	(2) Simultaneous vs C	2014	EUR	868	-0.0300	Dominated	10,850	106	99.4	0.788	1,177	-39, 238#	14,713
	(3) Sequential vs simultaneous	2014	EUR	-684	0.0200	Dominant	17,106	106	99.4	0.788	-928	-46, 392#	23,196
Sukhanova et al. 2009(154)	(1) Tailored	2009	USD	81	x	x	27	107.9	90.5	1	97	x	32
	(2) HOBI	2009	USD	184	x	x	61	107.9	90.5	1	219	x	73
	(C) Untailored	2009	USD	69	x	x	35	107.9	90.5	1	82	x	42
Other population													
Broekhuizen et al. 2015(126)	*mmol/l LDL cholesterol*	2010	EUR	-237	x	x	1,729	106	91.6	0.788	-349	x	2,544
	QALYs	2010	EUR	-237	-0.0016	145,899	x	106	91.6	0.788	-349	214, 686	x
Chatterton et al. 2018(164)	Healthcare persp.	2013	AUD	-856	0.0260	Dominant	x	107	96.1	1.472	-647	-24, 886#	x
	Soc. Persp.	2013	AUD	-2,591	0.0260	Dominant	x	107	96.1	1.472	-1,959	-75, 327#	x
Emmons et al. 2005(143)	Risk factor dropped	2005	USD	46	x	x	379	107.9	82.4	1	60	x	496
	Unit change	2005	USD	46	x	x	228	107.9	82.4	1	60	x	298

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Ethgen et al. 2016(128)	(1) 1 portion/ day lowest value range	2014	EUR	-221	0.0181	-12,237	x	108	99.4	0.768	-312	-17, 271	x
	(2) 2 portions/ day highest value range	2014	EUR	798	0.0065	123,122	x	108	99.4	0.768	1,126	173, 775	x
	(3) 3 portions/ day highest value range	2014	EUR	1,174	0.0086	136,244	x	108	99.4	0.768	1,657	192	x
	(1) 1 portion/day highest value range	2014	EUR	421	0.0045	94,304	x	108	99.4	0.768	594	133, 101	x
	(2) 2 portions/ day lowest value range	2014	EUR	88	0.0260	3,390	x	108	99.4	0.768	124	4,785	x
	(3) 3 portions/ day lowest value range	2014	EUR	407	0.0279	14,602	x	108	99.4	0.768	574	20, 609	x
Gillespie et al. 2017(129)	(a)	2006	EUR	-2,914	0.1050	missing	x	102	92.4	0.782	-4,107	-39, 111#	x
	(b)	2006	EUR	-126	-0.0340	missing	x	102	92.4	0.782	-178	5, 223#	x
	(c)	2006	EUR	-1,092	0.0090	missing	x	102	92.4	0.782	-1,539	-170, 992#	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Herman et al. 2014(147)	Direct costs	2008	CAD	302	0.0100	missing	x	107	90.1	1.203	299	29, 935#	x
	Soc. Costs	2008	CAD	-1,138	0.0100	missing	x	107	90.1	1.203	-1,128	-112, 802#	x
	Lost productivity costs	2008	CAD	-1,440	0.0100	missing	x	107	90.1	1.203	-1,427	-142, 738#	x
	Employer costs	2008	CAD	-1,187	0.0100	missing	x	107	90.1	1.203	-1,177	-117, 659#	x
Holt et al. 2018(130)	(1) Health-care costs EQ-5D	2015	GBP	870	0.0035	246,921	x	108	100	0.689	1,361	386, 269	x
	(2) Soc. Costs EQ-5D	2015	GBP	1,295	0.0035	367,543	x	108	100	0.689	2,026	574, 963	x
	(1) Health-care costs SF-6D	2015	GBP	870	0.0148	58,688	x	108	100	0.689	1,361	91, 808	x
	(2) Soc. Costs SF-6D	2015	GBP	1,295	0.0148	87,358	x	108	100	0.689	2,026	136, 658	x
Price et al. 2006(134)	Costs I	2006	GBP	21	x	x	missing	108	81.4	0.689	41	x	missing
	Costs C	2006	GBP	23	x	x	missing	108	81.4	0.689	44	x	missing
Sikand et al. 2000(152)	Net savings total	1996	USD	29,549	x	x	missing	107.9	66.2	1	48,145	x	missing
	Net savings pp	1996	USD	687	x	x	missing	107.9	66.2	1	1,120	x	missing
	Benefit-cost ratio	1996	USD	1	x	x	missing	107.9	66.2	1	2	x	missing
	Costs averted	1996	USD	4	x	x	missing	107.9	66.2	1	6	x	missing

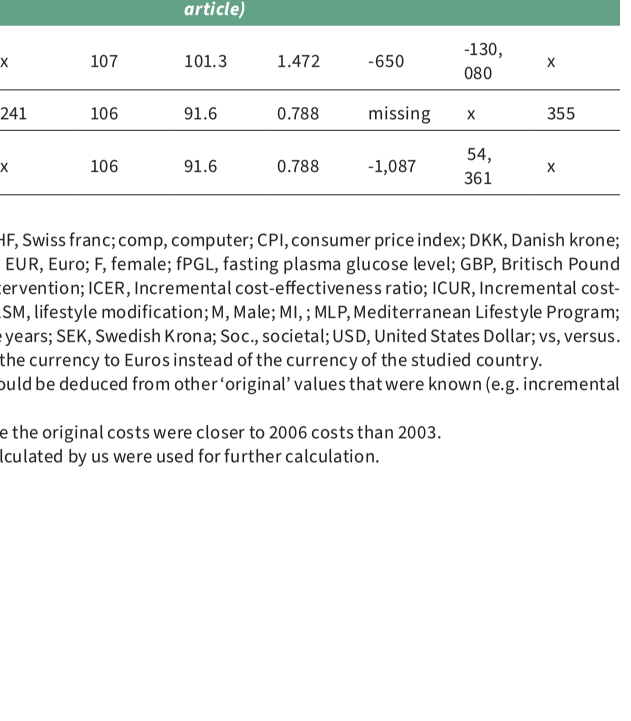
Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Speed et al. 2010(136)	(1) Personalized vs C	2010	GBP	-13	0.02	missing	x	108	90.1	0.689	-23	-1, 158#	x
Troyer et al. 2010(156)	(1) Meals only	2004	USD	2,619	0.0298	87,825	x	107.9	79.7	1	3,544	118, 856	x
	(2) MNT only	2004	USD	72	0.015	4,807	x	107.9	79.7	1	97	6,505	x
	(3) Meals + MNT	2004	USD	3,470	0.0208	166,980	x	107.9	79.7	1	4,696	225, 978	x
Walsh et al. 2015(138)	*QALYs*	2015	USD	3,000	missing	Dominated	x	107.9	79.7	1	4,060	Dominated	x
Walters et al. 2017(139)	I	2015	GBP	307	missing	missing	x	108	100	0.689	480	missing	x
Whigham et al. 2015(140)	I vs C (I)	2015	GBP	missing	0.0295	3,052	x	108	100	0.689	141#	4,775	x
	I vs C (C)	2015	GBP	missing	0.0261	missing	x	108	100	0.689	x	x	x
	Total	2015	GBP	12,418	missing	missing	x	108	100	0.689	19,426	x	x
Malnourished													
Lorefält et al. 2011(132)	I	2007	EUR	1,005	x	x	missing	105.0*	87.4*	0.692*	1,745	x	missing
	C	2007	EUR	921	x	x	missing	105.0*	87.4*	0.692*	1,599	x	missing
Milte et al. 2016(165)	QALYs	2010	AUD	567	0.0200	28,350	x	107	89.3	1.472	461	23, 061	x
van der Pols-Vijlbrief et al. 2017(133)	Gain in kg	2014	EUR	-274	x	x	-741	106	99.4	0.788	-372	x	-1,005
	QALYs	2014	EUR	-274	0.0085	-32,173	x	106	99.4	0.788	-372	-43, 627	x

Study	Costs/effects intervention/ perspective	Year costs	Currency article	Costs in article	QALYs	ICUR in article	ICER in article	CPI (2019)	CPI (year cost article)	PPP	Cost (2019 USD)	ICUR 2019 USD	ICER 2019 USD
Sharma et al. 2018(166)	QALYs	2016	AUD	-907	0.0050	Domi-nant	x	107	101.3	1.472	-650	-130, 080	x
Wyers et al. 2013(141)	Gain in kg	2010	EUR	missing	x	x	241	106	91.6	0.788	missing	x	355
	QALYs	2010	EUR	-739#	-0.02	36,943	x	106	91.6	0.788	-1,087	54, 361	x

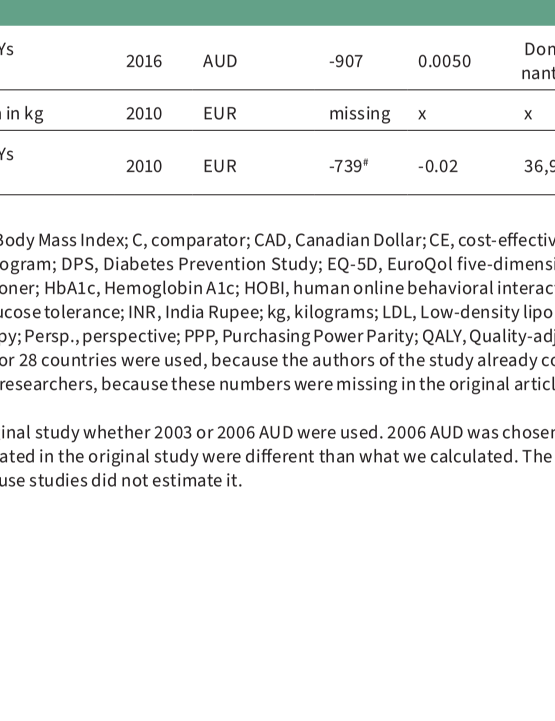
AUD, Australian Dollar; BMI, Body Mass Index; C, comparator; CAD, Canadian Dollar; CE, cost-effectiveness; CHF, Swiss franc; comp, computer; CPI, consumer price index; DKK, Danish krone; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; EQ-5D, EuroQol five-dimension scale; EUR, Euro; F, female; fPGL, fasting plasma glucose level; GBP, Britisch Pound Sterling; GP, general practitioner; HbA1c, Hemoglobin A1c; HOBI, human online behavioral interaction; I, intervention; ICER, Incremental cost-effectiveness ratio; ICUR, Incremental cost-utility ratio; IGT, Impaired glucose tolerance; INR, India Rupee; kg, kilograms; LDL, Low-density lipoprotein; LSM, lifestyle modification; M, Male; MI, ; MLP, Mediterranean Lifestyle Program; MNT, Medical nutrition therapy; Persp., perspective; PPP, Purchasing Power Parity; QALY, Quality-adjusted life years; SEK, Swedish Krona; Soc., societal; USD, United States Dollar; vs, versus.
*Overall European PPP/CPI for 28 countries were used, because the authors of the study already converted the currency to Euros instead of the currency of the studied country.
#Numbers calculated by the researchers, because these numbers were missing in the original article. They could be deduced from other 'original' values that were known (e.g. incremental costs and effects).
^It was unclear from the original study whether 2003 or 2006 AUD were used. 2006 AUD was chosen, because the original costs were closer to 2006 costs than 2003.
+ The QALYs that were calculated in the original study were different than what we calculated. The QALYs calculated by us were used for further calculation.
x No information given because studies did not estimate it.

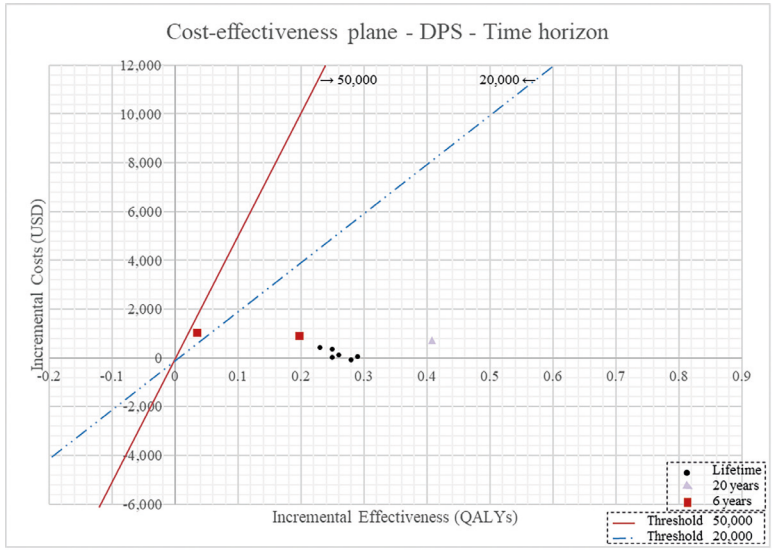
Appendix 2.8: Cost-effectiveness plane DPP and DPS studies

1. All DPP and DPS studies

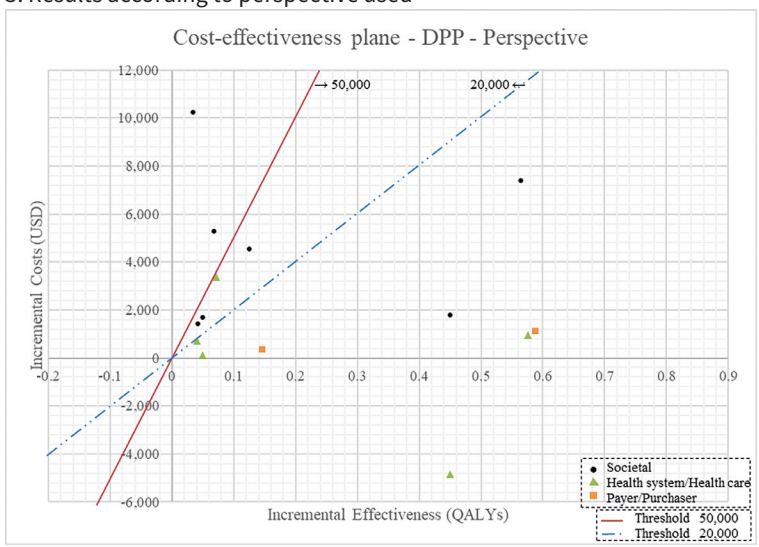


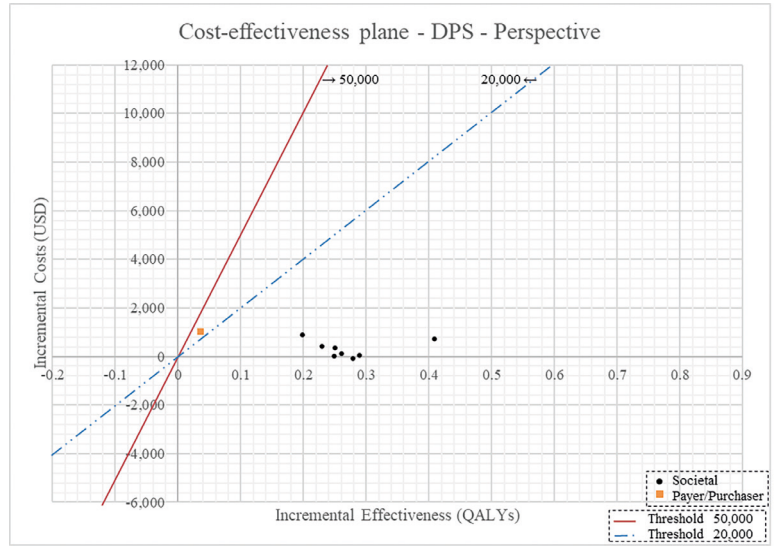
2. Results according to time horizon used



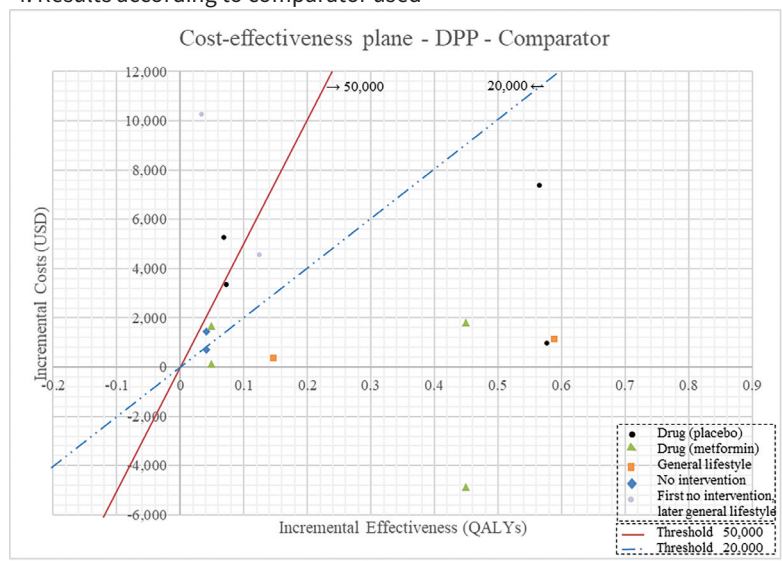


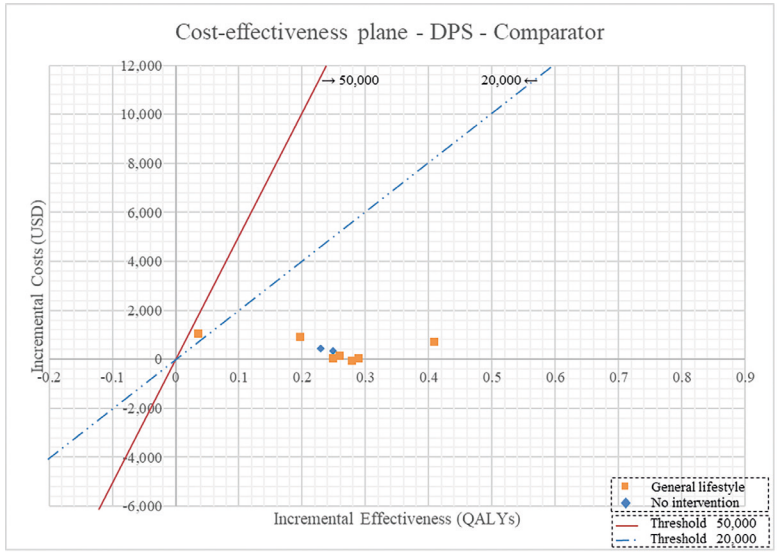
3. Results according to perspective used



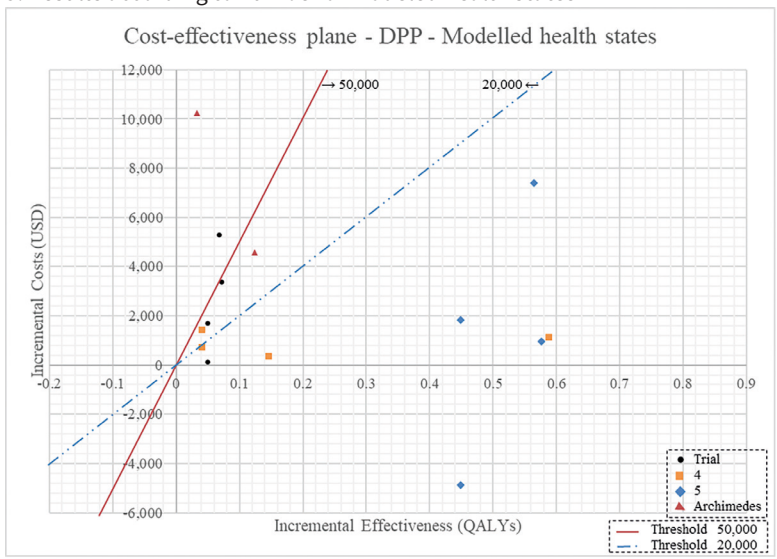


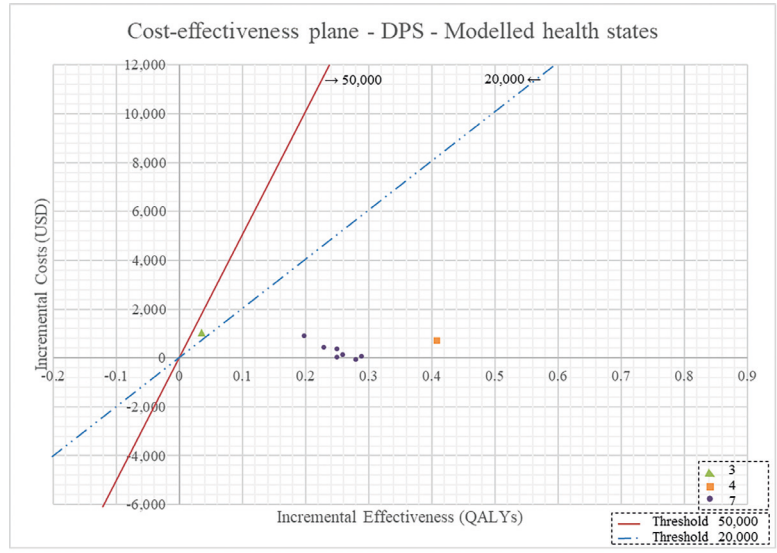
4. Results according to comparator used



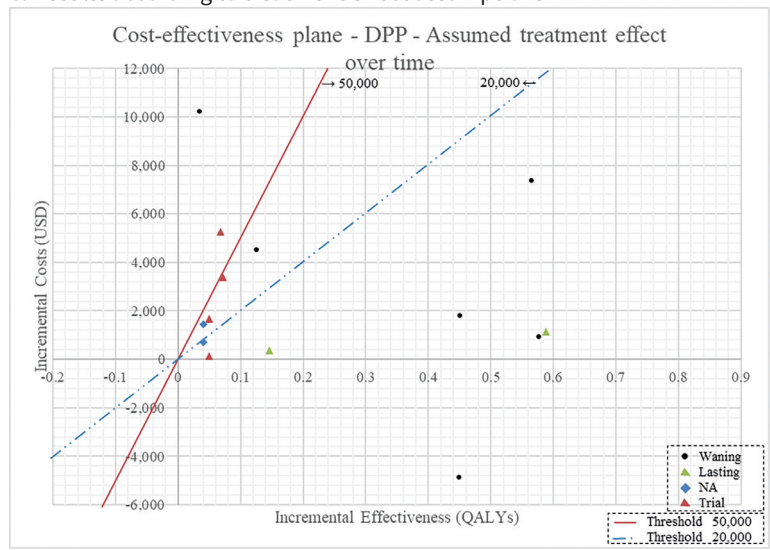


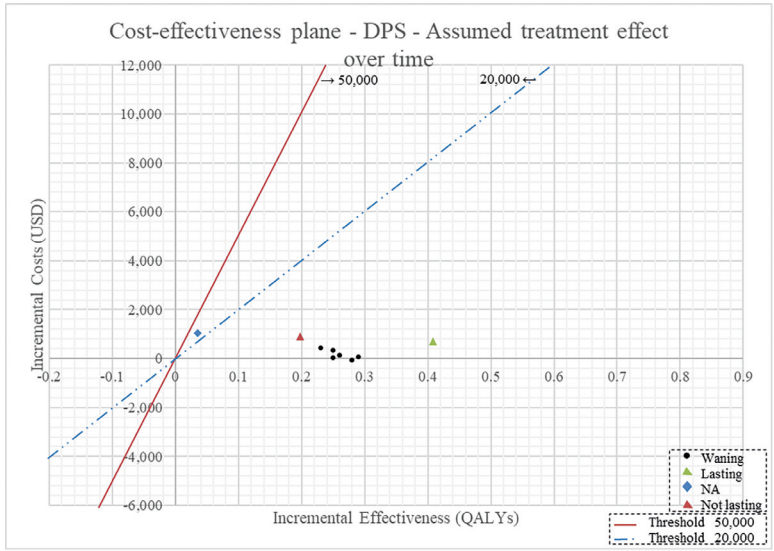
5. Results according to number of modeled health states



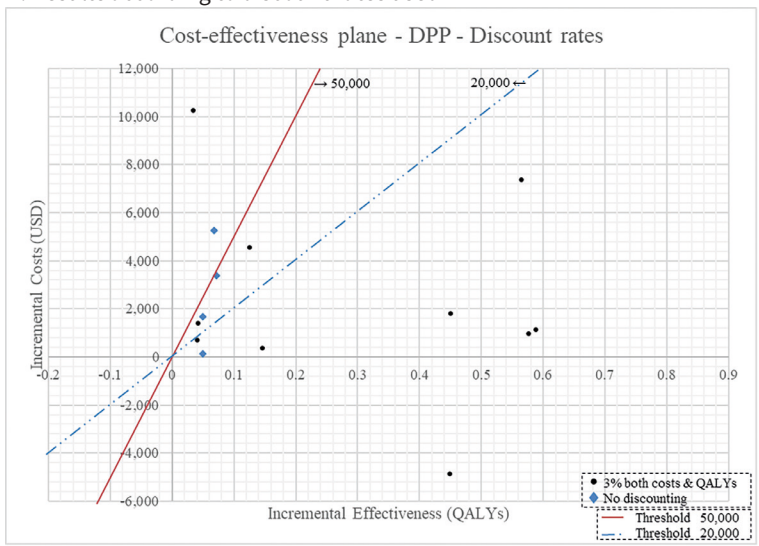


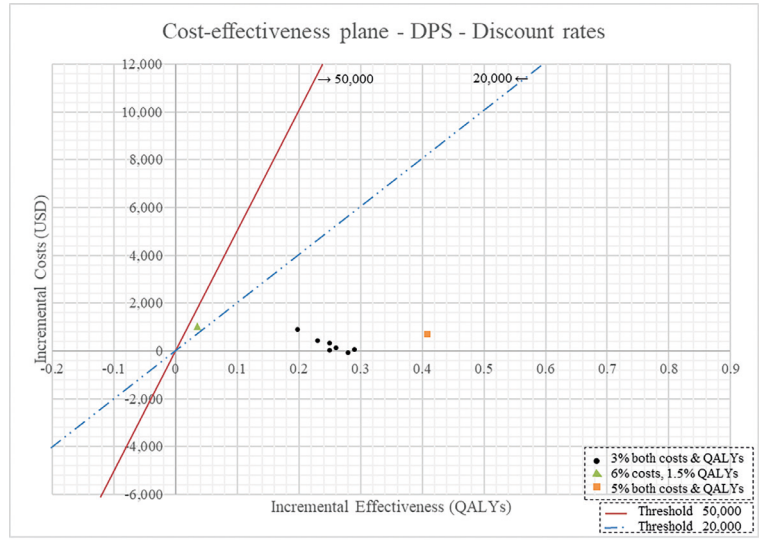
6. Results according to treatment effect assumptions





7. Results according to discount rates used





Appendix 2.9: Reporting according to the CHEERS checklist

	Item number	Ackermann et al. 2006(112)	Avenell et al. 2004(119)	Caro et al. 2004(113)	Dalziel et al. 2007(158)	Eddy et al. 2005(114)	Galani et al. 2007(109)	Herman et al. 2005(116)	Icks et al. 2007(131)	Lindgren et al. 2003(117)	Lindgren et al. 2007(118)	Palmer et al. 2004(108)	Ramachandran et al. 2007(115)	Smith et al. 2016(153)	The Diabetes prevention program 2003(104)	Barton et al. 2009(125)	Befort et al. 2010(142)	Franz et al. 1995(144)	Glasgow et al. 1997(145)	Goldfield et al. 2001(146)	Kaphlan et al. 1987(105)	McConnon et al. 2007(106)	Olsen et al. 2005(111)	Redman et al. 2017(151)
Title and abstract																								
Title	1	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	N
Abstract	2	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N
Introduction																								
Background and objectives	3	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	N
Methods																								
Target population and subgroups	4	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	5	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Study perspective	6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N
Comparators	7	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Discount rate	9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	N	N
Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Measurement of effectiveness	11a	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	11b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	N	-	-	-	-	-	-	-	-	-	-
Measurement and valuation of preference- based outcomes	12	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	Y	N	N	N	N	N	Y	N	N
Estimating resources and costs	13a	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	Y	N	Y	Y	Y	Y	N
	13b	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	-
Currency, price date and conversion	14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	N
Choice of model	15	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	-
Assumptions	16	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	-
Analytical methods	17	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	N	N	Y	N	Y	Y	N	Y	Y	Y

Results																										
Study parameters	18	N	N	Y	N	N	N	Y	Y	N	N	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N		
Incremental costs and outcomes	19	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N		
Characterizing uncertainty	20a	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	N	Y	N	N	Y	Y	Y	N		
	20b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	-	-	-	-	-	-	-	-	-	-		
Characterizing heterogeneity	21	Y	N	N	N	Y	Y	Y	N	Y	N	Y	N	N	N	N	N	Y	N	N	N	N	Y	N		
Discussion																										
Study findings, limitations, generalizability, and current knowledge	22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N		
Other																										
Source of funding	23	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N		
Conflict of interests	24	-	Y	Y	-	Y	-	Y	Y	-	-	-	-	Y	-	Y	Y	-	Y	-	-	Y	-	-		

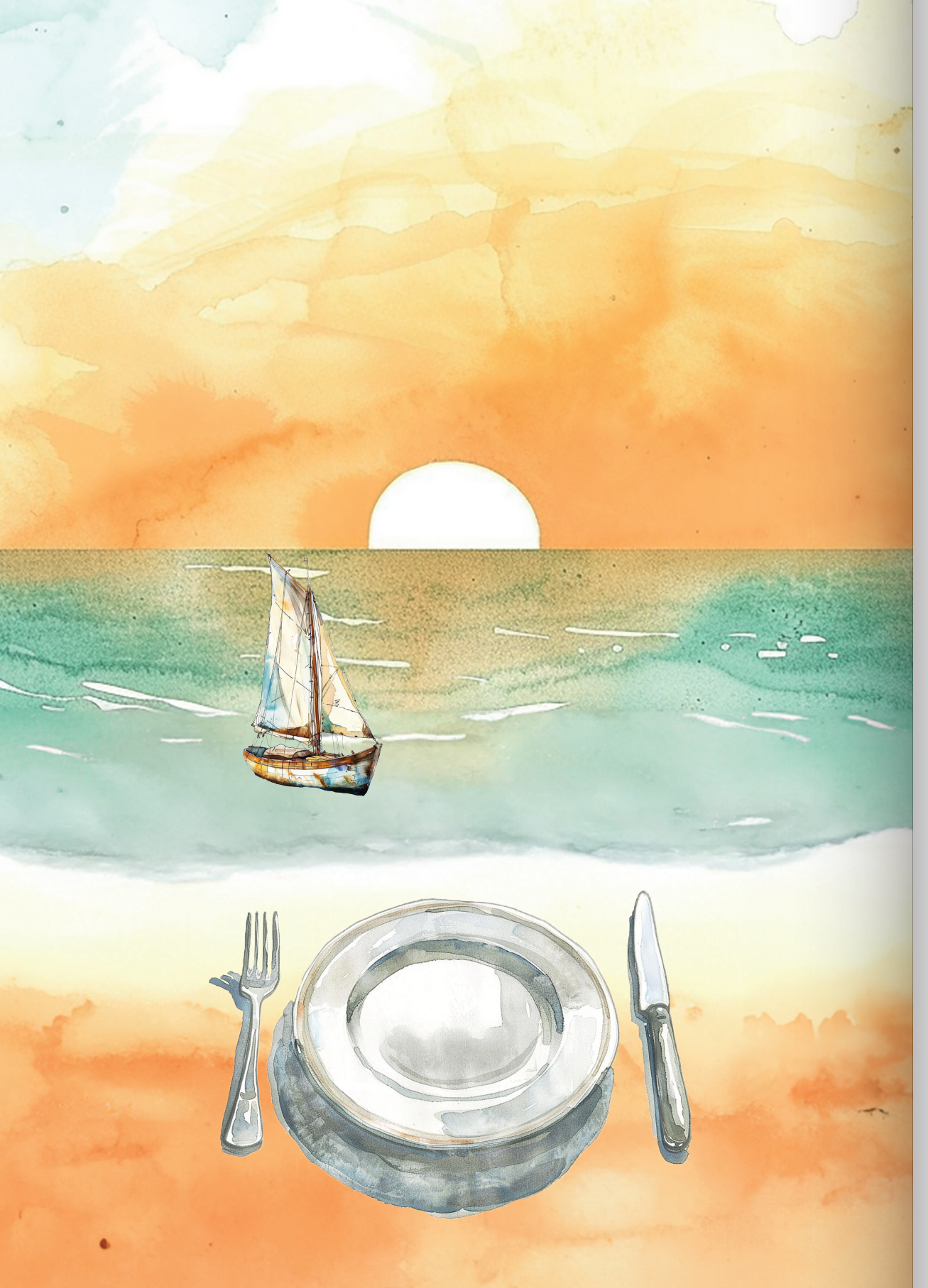
Item number		**Segal et al. 1998**(110)	**Sherwood et al. 2006**(107)	**Toobert et al. 2007**(155)	**Wylie-Rosett et al. 2001**(157)	**Leigh et al. 1992**(149)	**Schulz et al. 2014**(135)	**Sukhanova et al. 2009**(154)	**Broekhuizen et al. 2015**(126)	**Chatterton et al. 2018**(164)	**Emmons et al. 2005**(143)	**Ethgen et al. 2016**(128)	**Gillespie et al. 2017**(129)	**Herman et al. 2014**(147)	**Holt et al. 2018**(130)	**Price et al. 2006**(134)	**Sikand et al. 2000**(152)	**Speed et al. 2010**(136)	**Troyer et al. 2010**(156)	**Walsh et al. 2015**(138)	**Walters et al. 2017**(139)	**Whigham et al. 2015**(140)	**Lorefält et al. 2011**(132)	**Milte et al. 2016**(165)	**Van der Pols-Vijlbrief et al. 2017**(133)	**Sharma et al. 2018**(166)	**Wyers et al. 2013**(141)
Title and abstract																											
Title	1	Y	N	N	N	N	Y	N	Y	Y	N	Y	Y	Y	N	N	N	N	Y	N	N	N	N	Y	Y	Y	Y
Abstract	2	Y	Y	N	N	N	Y	N	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	Y	Y	Y	Y
Introduction																											
Background and objectives	3	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods																											
Target population and subgroups	4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Setting and location	5	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	6	N	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Comparators	7	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Discount rate	9	Y	N	N	N	N	Y	N	N	Y	N	Y	Y	Y	Y	N	N	N	Y	N	N	N	N	Y	Y	Y	N
Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Measurement of effectiveness	11a	-	Y	Y	Y	N	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
	11b	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Measurement and valuation of preference based outcomes	12	N	N	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Estimating resources and costs	13a	-	Y	N	Y	N	Y	Y	Y	Y	Y	-	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	13b	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Currency, price date and conversion	14	N	N	N	N	N	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Y	Y	Y	Y	Y
Choice of model	15	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Assumptions	16	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Analytical methods	17	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results																											
Study parameters	18	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	N	Y	N	N	Y	Y	Y	N
Incremental costs and outcomes	19	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	Y	Y	Y	N
Characterizing uncertainty	20a	-	Y	N	N	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	N	N	N	Y	N	Y	N	N	Y	Y	Y	Y
	20b	Y	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Characterizing heterogeneity	21	Y	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y

Discussion																										
Study findings, limitations, generalizability, and current knowledge	22	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Other																										
Source of funding	23	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Conflict of interests	24	N	N	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y

N, Not fulfilled; Y, Fulfilled; - ,Not Applicable



Chapter 3

The lifetime health and economic burden of obesity in five European countries: what is the potential impact of prevention?

Martine E.J.I. Hoogendoorn, Milanne M.J. Galekop, Pieter H.M. van Baal

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ABSTRACT

Objectives

Estimating the burden of obesity in five European countries (Germany, Greece, the Netherlands, Spain, and the UK) and the potential health benefits and changes in healthcare costs associated with a reduction in body mass index (BMI).

Methods

A Markov model was used to estimate the long-term burden of obesity. Health states were based on the occurrence of diabetes, ischemic heart disease and stroke. Multiple registries and literature sources were used to derive the demographic, epidemiological, and cost input parameters. For the base-case analyses, the model was run for a starting cohort of healthy obese people with a BMI of 30 and 35 kg/m^2 aged 40 years to estimate the lifetime impact of obesity and the impact of a one-unit decrease in BMI. Different scenario and sensitivity analyses were performed.

Results

The base-case analyses showed that total lifetime healthcare costs (for obese people aged 40 and BMI 35 kg/m^2) ranged from €75,376 in Greece to €343,354 in the Netherlands, with life expectancies ranging from 37.9 years in Germany to 39.7 years in Spain. A one-unit decrease in BMI showed gains in life expectancy ranging from 0.65 to 0.68 year and changes in total healthcare costs varying from -€1,563 to +€4,832.

Conclusions

The economic burden of obesity is substantial in the five countries. Decreasing BMI results in health gains, reductions in obesity-related healthcare costs, but an increase in non-obesity related healthcare costs, which emphasizes the relevance of including all costs in decision making on implementation of preventive interventions.

INTRODUCTION

The prevalence of obesity in Europe is high and increasing over time. In 2014, 51.1% of the adult EU members was overweight defined as a body mass index (BMI) of ≥ 25 kg/m^2, of which 15.4% could be classified as obese (BMI ≥ 30 kg/m^2) (192). These values increased to 52.7% and 16.3%, respectively in 2019 (193), and are expected to increase even more because of a continuing increase in intake of energy-dense foods and a decrease in physical activity (194). Obesity is a major risk factor for diabetes, cardiovascular disease (heart disease and stroke), several types of cancer and musculoskeletal disorders (194). According to the Global Burden of Disease Study (GBD), a high BMI was associated with 4.7 million deaths and 147.7 million disability-adjusted life years worldwide in 2017 (195). Consequently, obesity is associated with substantial healthcare costs for treating obesity-related diseases and complications (87,196,197), and other costs (e.g., lost productivity) (198,199).

A review from Tremmel et al. (87) showed that most of the studies investigating the economic burden of obesity included costs associated with treating obesity-related diseases and some included costs related to loss of productivity and premature mortality. However, costs related to informal care, defined as unpaid care provided by people other than healthcare professionals, were not considered in any of the studies in the review. Two recently published studies on the economic burden of obesity included short-term costs for informal care (200,201). Consideration of the long-term costs of informal care is relevant because obese people receive more informal care than people with normal weight (202).

Besides investigating the economic burden of obesity, several studies explored the impact of a reduction in BMI or the reduction in percentage of people with obesity on health and costs, concluding that a reduction in obesity prevalence is associated with cost savings in obesity-related costs (203,204). Other studies investigating the cost-effectiveness of treatments for obesity concluded that treatments are cost-effective or cost saving based on the change in costs for obesity-related diseases and complications (205–207). However, because high BMI is associated with an increased mortality risk (208), a reduction in BMI will result in an increase in life expectancy with a certain risk for getting other non-obesity-related diseases requiring treatment and thus costs in these additional years lived (209–211). Reducing high BMI might therefore lead to a reduction in costs for obesity-related diseases, but these savings might be (partly) compensated by the additional healthcare costs for other diseases in life years gained (212). All relevant healthcare costs should therefore be included in an analysis to show the full lifetime impact of an intervention that reduces BMI.

The aim of the current study was to estimate the long-term burden of obesity in five European countries, including Germany, Greece, the Netherlands, Spain, and the UK by presenting a wide range of health outcomes and healthcare costs using a newly developed obesity model. In addition, the study aimed to assess the potential health benefits and changes in healthcare costs associated with a reduction in high BMI to normal values because

of a hypothetical health intervention. Costs included in the model were lifetime medical costs for obesity-related diseases, informal care costs, and medical costs for other diseases.

METHODS

Model structure

To model the impact of obesity on health and lifetime costs, a health economic model was developed as part of the COMPAR-EU project, a project that aimed to estimate the (cost-) effectiveness of self-management interventions for obesity and included partners from five different countries (Germany, Greece, the Netherlands, Spain, and the UK) (213). The developed Markov model included obesity-related diseases as health states and had a cycle length of 1 year. Figure 3.1 shows the model structure. Besides the death state, the following health states were included: diabetes, ischemic heart disease (IHD) and stroke. These obesity states were included in the model, as, compared with other obesity-related diseases, prevalence and costs of these diseases were the highest (214,215). The first state included obese people without any of the three diseases, but who are at risk to develop diabetes, IHD or stroke depending on their BMI. When patients have developed one of the three diseases, they have a higher risk for one of the other diseases. Therefore, all possible combinations of diseases were modeled; patients could have one disease, combinations of two diseases or all three diseases combined. The impact of other obesity-related diseases than diabetes, IHD and stroke was not explicitly modeled but had been included through the impact on mortality.

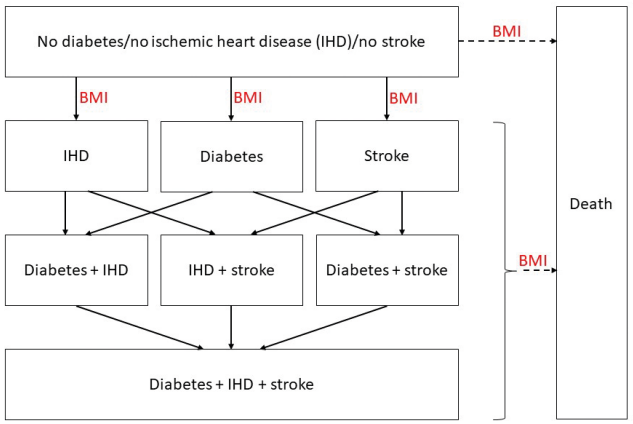


Figure 3.1: Structure of the Markov model for obesity. BMI, body mass index; IHD, ischemic heart disease.

Transition rates between health states reflected the incidence of disease(s), while mortality rates for the population without disease(s) and for patients with disease(s) reflected the

transition probabilities from the health states to death. Occurrence of diseases and mortality were dependent on BMI, which was modeled continuously.

The model starts with an obese population specified by sex, age and mean BMI. The model then simulates the changes in this cohort over time because of occurrence of diabetes, IHD and stroke, and death. The time horizon of the model was lifetime, which means that subjects were followed up to the age of 100, after which they are assumed to die in the next cycle. Transition rates were not fixed, as both incidences of diseases and mortality were dependent on sex, age and BMI and being in a certain health state (e.g., incidence of IHD is higher for patients in the diabetes state than patients in the no diabetes/IHD/stroke state). Mortality in the diabetes state was a combination of mortality attributable to diabetes plus mortality because of other causes. For IHD, including myocardial infarction and for stroke, which are events with a high risk for mortality at the time of occurrence, mortality has been separated in case-fatality, mortality attributable to either IHD or stroke and mortality because of other causes. The case-fatality rate was applied to the new incident cases, which implies that from the new incident cases of IHD or stroke, a certain proportion was assumed to die immediately. Mortality attributable to either IHD or stroke was applied to patients in the 'stable' state, that is, these mortality rates were applied only to people who did not die from IHD or stroke immediately.

Each health state was associated with a certain value for quality of life (QOL) and costs. QOL values were specified by sex, age and disease status. Costs included in the model were all healthcare related costs (in 2020 euros[1]), including medical costs for diabetes, IHD and stroke, informal care costs, and medical costs for other diseases. The model was implemented in R using RStudio (version Ri386 3.6.1/Rx64 3.6.1).

Model inputs

Multiple sources from registries and literature were used to derive the demographic, epidemiological, and cost input parameters. All details on the input parameters are presented in Appendix 3.1. The mean BMI by sex and age for the different countries was obtained from the GBD (216). Relative risks (RRs) for the association between BMI and all-cause mortality, specified by sex, were obtained from a meta-analysis of 230 cohort studies (208), while RRs for the association between BMI and diabetes, IHD and stroke, specified by age, were obtained from the GBD (216). In addition, RRs for the co-occurrence of 'diabetes and stroke', 'diabetes and IHD' and 'IHD and stroke' were included to take into account that the three diseases tend to cluster (217–219). The prevalence and incidence for diabetes, IHD and stroke, specified by sex and age for the five European countries, were obtained from the DYNAMO-HIA study (217,218). Mortality data were based on the DYNAMO-HIA study (217,218), two studies by Vaartjes et al. (220,221) one study by Hoogenveen et al. (222) and OECD data (223,224). QOL data were

1 The Consumer Price Index was used to calculate prices of goods and services in a country over time and the Purchasing Power Parity was used as currency conversion rate to convert prices/expenditures expressed in national currency to other currencies.

based on general population sex- and age-specific utilities derived from the EQ-5D, which is a generic health-related QOL measure (225), and adjusted for the occurrence of diabetes, IHD and stroke using prevalence data and previously published utility decrements for the different diseases (226). Medical costs for treating diabetes, IHD and stroke were obtained from different country-specific literature sources (227–238). Medical costs for other diseases in the Netherlands and the UK, were obtained from the Dutch PAID tool version 3 and UK PAID tool version 1, respectively (239,240). For the other three countries these costs were calculated by subtracting the obesity-related costs per capita for diabetes, IHD and stroke from the annual healthcare spending per capita by sex and age (241–243). See the study of Mokri et al. (244) for the complete description of this cost calculation.

Model analyses

For the base case analyses, the model was run for a cohort aged 40 years at the start of the simulation (50% women) with either a BMI of 30 kg/m^2 or a BMI of 35 kg/m^2 to show the impact of different levels of BMI on health outcomes and costs. In addition, the impact of a one-unit decrease in BMI was explored by comparing lifetime results for a cohort with starting BMI of 30 kg/m^2 with the results of a cohort with a BMI of 29 kg/m^2. Furthermore, results for a cohort with BMI 35 kg/m^2 were compared with a cohort with BMI 34 kg/m^2 to show the impact of the starting level of BMI on changes in health outcomes and costs. Outcomes predicted by the model were: life expectancy, years with diabetes, incident cases of obesity-related diseases, quality-adjusted life years (QALYs), and different types of costs from an extended healthcare perspective. Costs and effects were not discounted in the base-case analyses to increase comparability between countries (Appendix 3.3 shows the discounted results).

Scenario analyses

In addition, two scenario analyses were performed to show the effects and costs attributable to obesity and the potential impact of prevention. The first scenario was performed by comparing the results of an obese cohort (BMI 35 kg/m^2) aged 40 years at the start of the simulation (50% women) with the results of a cohort with BMI 25 kg/m^2 (i.e., lowest BMI in the overweight range) aged 40 years at the start of the simulation (50% women). The second scenario was performed on a population level using the obese population aged 25-65 years in the five countries as a starting point for the simulation. For this scenario, we first estimated the total numbers of obesity cases in the specific countries; the general population by sex and age in a specific country, was combined with sex- and age-specific percentages of obesity (192,193). Next, the total numbers of obese cases (with information about BMI, sex and age) were used to calculate the mean BMI, the percentage of women, and mean age of the obese population, which were used as inputs for the model. Lifetime results for the obese population in the different countries were then compared with results for a population comparable in sex and age, but with a BMI of 25 kg/m^2 to show the potential of prevention on a population level.

Sensitivity analyses

To translate uncertainty around the input parameters into uncertainty around the outcomes of the model, probabilistic sensitivity analyses (PSA) were performed for the scenario analyses. Uncertainty around the RRs for the association of BMI with all-cause mortality and the RRs for BMI and obesity-related diseases was included as well as uncertainty around costs. The other parameters were kept fixed. Appendix 3.2 shows additional information on the PSA.

In addition, several one-way sensitivity analyses (SA) were performed for all countries to estimate the impact of key model parameters or assumptions on the outcomes. The first SA used a time horizon of 20 years instead of lifetime. In the second SA, RRs for the association between BMI and obesity-related diseases were obtained from DYNAMO-HIA (217,218) instead of the GBD. The third SA explored the impact of using RRs for the association between BMI and all-cause mortality based on DYNAMO-HIA (217,218) instead of the meta-analysis of Aune et al. (208) In the fourth SA, no increased risk for the co-occurrence of diabetes and stroke and diabetes and IHD was assumed to be conservative. In the fifth SA, productivity costs were added calculated using the SHARE data (245). Productivity costs are costs because of missing work or productivity because of illness or health conditions related to obesity, specified by BMI. The last SA added productivity- and age-specific non-medical costs, resulting in an analysis from an extended societal perspective. Non-medical costs were estimated from national household consumption/expenditure surveys in each country considering the household size (246–250). These costs were included as living longer results in more opportunity to consume other goods and services, such as electricity, gas, housing and water (210,244). More details about the productivity- and non-medical costs can be found in Appendix 3.1.

Model validation

The model was validated by running a cohort of men/women with a starting age of 40 years and a mean BMI of the general population as was observed in each country (216). The resulting life expectancy was compared with the life expectancy for men and women for the different countries reported by EUROSTAT (251). In a second analysis, the model results were compared with outcomes of other obesity models in the literature (252,253) by comparing the predicted difference in life expectancy between a healthy and obese 40-year-old person.

RESULTS

Table 3.1 shows the lifetime results for cohorts with a starting age of 40 years and a mean BMI level of 30 or 35 kg/m^2. For both cohorts, Spain had the highest life expectancy. Total lifetime healthcare costs in a cohort with BMI level of 35 kg/m^2, ranged from €75,376 (Greece) to €343,354 (the Netherlands). In general, total costs were higher in the cohort of people with a BMI of 35 kg/m^2 compared with a BMI of 30 kg/m^2. In most countries, medical costs for other diseases had the largest contribution to the total costs.

Table 3.2 shows that a reduction of one unit in BMI for a cohort of 35 kg/m² resulted in a higher gain in life expectancy and reduction in disease cases compared with a cohort of 30 kg/m² in most countries. The savings in medical costs for diabetes, IHD and stroke were lowest in Greece and highest in Germany. In the Netherlands, an increase in total costs was observed, mainly because of the change in medical costs for other diseases. When the results of Tables 3.1 and 3.2 were discounted (see Appendix 3.3), medical costs for other diseases still appeared to have the largest contribution to the total costs, but to a lesser extent.

Table 3.3 shows the results of the scenario analyses. On a population level, the reduction of the BMI to healthy levels will result in cost savings in all countries in medical costs for obesity-related diseases, ranging from €8,532 in Greece to €22,042 per person in Germany. Moreover, there was a gain in life expectancy and QALY in all countries, but this gain was lower than in the cohort analyses. Because of this increase in life expectancy, the risk for getting other non-obesity-related diseases (including costs) increased as well. The increase in costs for non-obesity-related diseases was larger in the cohort analyses because the gain in life expectancy was higher. Total healthcare costs decreased in all countries, except for the Netherlands.

Table 3.4 shows the results of the SAs in the UK cohort. Health outcomes appeared to be most sensitive to the time horizon used (0.625 and 0.545 less gain in life expectancy and QALYs, respectively when SA1 was compared with the base case). Including productivity costs (SA5) did not change the total costs much (€52 difference when SA5 was compared with base case), whereas adding non-medical costs as well (SA6) considerably changed the total costs (€7,316 difference). The results of SAs in other countries showed comparable impact and are presented in Appendix 3.4.

Table 3.1: Lifetime results (per person) for the base-case analysis for a healthy cohort (starting age of 40 years) and different BMI levels in the absence of any weight loss intervention, costs in 2020 euros (undiscounted).

BMI	Outcome	Germany	Greece	Netherlands	Spain	UK
30 kg/m²	**Life expectancy (years)**	40.7	41.3	40.9	42.5	41.3
	Years with diabetes	5.0	4.3	6.3	7.1	3.3
	Cum. incident cases IHD /1000	331	194	375	204	338
	Cum. incident cases stroke /1000	280	557	294	288	317
	QALY	35.4	34.2	35.3	36.1	33.1
	Medical costs diabetes, IHD, stroke	€ 59,027	€ 22,895	€ 35,464	€ 29,894	€ 42,917
	Medical costs for other diseases	€ 204,807	€ 17,016	€ 312,588	€ 88,557	€ 109,361

Table 3.1: Continued.

BMI	Outcome	Germany	Greece	Netherlands	Spain	UK
	Informal care costs	€ 17,480	€ 29,737	€ 17,977	€ 48,193	€ 31,839
	Total costs	**€ 281,314**	**€ 69,648**	**€ 366,031**	**€ 166,633**	**€ 184,117**
35 kg/m²	**Life expectancy (years)**	37.9	38.6	38.1	39.7	38.6
	Years with diabetes	10.5	8.3	12.1	13.4	6.9
	Cum. incident cases IHD /1000	418	246	463	275	406
	Cum. incident cases stroke /1000	354	604	382	365	382
	QALY	32.6	31.7	32.5	33.3	30.6
	Medical costs diabetes, IHD, stroke	€ 87,535	€ 33,121	€ 56,487	€ 47,853	€ 60,846
	Medical costs for other diseases	€ 184,443	€ 16,644	€ 271,619	€ 83,995	€ 98,976
	Informal care costs	€ 14,837	€ 25,612	€ 15,248	€ 41,344	€ 27,178
	Total costs	**€286,814**	**€ 75,376**	**€ 343,354**	**€ 173,183**	**€ 187,000**

Abbreviations: BMI, body mass index; cum., cumulative; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year.

Table 3.2: Lifetime results (per person) for the base-case analysis of one unit decrease in BMI for a cohort age 40 years, costs in 2020 euros (undiscounted).

BMI	Outcome	Germany	Greece	Netherlands	Spain	UK
30 kg/m²	**Gain in life expectancy (years)**	0.363	0.360	0.371	0.379	0.347
	Decrease in years with diabetes	0.737	0.567	0.839	0.941	0.470
	Decrease in cum. incident cases IHD /1000	15	9	16	12	13
	Decrease in cum. incident cases stroke /1000	12	11	15	13	12
	Gain in QALY	0.376	0.348	0.390	0.396	0.322
	Change in medical costs diabetes, IHD, stroke	€ -4,327	€ -1,608	€ -3,174	€ -2,704	€ -2,863
	Change in medical costs for other diseases	€ 2,879	€ 49	€ 6,209	€ 637	€ 1,377

Table 3.2: Continued.

BMI	Outcome	Germany	Greece	Netherlands	Spain	UK
	Change in informal care costs	€ 378	€ 597	€ 406	€ 990	€ 656
	Change in total costs	**€ -1,072**	**€ -961**	**€ 3,441**	**€ -1,076**	**€ -829**
35 kg/m²	**Gain in life expectancy (years)**	0.675	0.645	0.658	0.677	0.657
	Decrease in years with diabetes	1.338	0.960	1.370	1.487	0.874
	Decrease in cum. incident cases IHD /1000	19	11	18	16	14
	Decrease in cum. incident cases stroke /1000	17	8	20	17	14
	Gain in QALY	0.692	0.611	0.681	0.696	0.598
	Change in medical costs diabetes, IHD, stroke	€ -6,744	€ -2,369	€ -4,914	€ -4,207	€ -4,147
	Change in medical costs for other diseases	€ 4,735	€ 91	€ 9,129	€ 1,073	€ 2,520
	Change in informal care costs	€ 610	€ 946	€ 617	€ 1,573	€ 1,086
	Change in total costs	**€ -1,398**	**€ -1,332**	**€ 4,832**	**€ -1,563**	**€ -539**

Abbreviations: BMI, body mass index; cum., cumulative; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year.

Table 3.3: Lifetime results scenario analyses (per person) (95% uncertainty interval), costs in 2020 euros (undiscounted).

Outcome	Germany	Greece	Netherlands	Spain	UK
Cohort (40 years, BMI 35 kg/m2), decrease BMI to 25kg/m2					
Gain in life expectancy (years)	3.88 (3.66; 4.11)	3.82 (3.60; 4.05)	3.92 (3.71; 4.13)	4.00 (3.80; 4.22)	3.73 (3.51; 3.97)
Gain in QALY	4.04 (3.86; 4.23)	3.70 (3.54; 3.87)	4.14 (3.97; 4.32)	4.22 (4.06; 4.39)	3.48 (3.31; 3.65)
Change in medical costs diabetes, IHD, stroke	€ -45,994 (-56,012; -37,968)	€ -16,756 (-21,102; -13,367)	€ -33,584 (-42,156; -26,182)	€ -28,747 (-36,136; -22,995)	€ -30,022 (-36,632; -24,632)
Change in medical costs for other diseases	€ 29,137 (18,797; 42,895)	€ 522 (181; 994)	€ 61,063 (40,371; 87,660)	€ 6,538 (3,840; 10,394)	€ 14,511 (9,586; 20,883)
Change in informal care costs	€ 3,821 (2,434; 5,481)	€ 6,041 (3, 851; 8,626)	€ 4,062 (2,586; 5,819)	€ 10,020 (6,372; 14,319)	€ 6,673 (4,261; 9,581)
Change in total costs	**€ -13,036 (-28,306; 3,781)**	**€ -10,192 (-14,679; -6,097)**	**€ 31,541 (8,394; 59,697)**	**€ -12,189 (-20,433; -4,081)**	**€ -8,838 (-17,683; -150)**
Obese population, 25-65 years, decrease BMI to 25 kg/m2					
Gain in life expectancy (years)	1.70 (1.48; 1.92)	1.76 (1.54; 1.97)	1.77 (1.57; 1.97)	1.82 (1.62; 2.03)	1.71 (1.48; 1.94)
Gain in QALY	1.74 (1.56; 1.92)	1.71 (1.55; 1.87)	1.85 (1.69; 2.01)	1.89 (1.73; 2.05)	1.62 (1.46; 1.78)
Change in medical costs diabetes, IHD, stroke	€ -22,042 (-26,764; -17,975)	€ -8,532 (-10,500; -6,942)	€ -15,405 (-19,108; -12,397)	€ -13,391 (-16,668; -10,720)	€ -16,663 (-20,363; -13,549)
Change in medical costs for other diseases	€ 13,563 (8,614; 20,093)	€ 225 (83; 417)	€ 31,100 (20,388; 45,319)	€ 3,029 (1,766; 4,748)	€ 6,797 (4,376; 9,752)
Change in informal care costs	€ 1,813 (1,170; 2,637)	€ 3,050 (1,975; 4,460)	€ 2,069 (1,344; 3,002)	€ 4,851 (3,142; 7,075)	€ 3,393 (2,189; 4,940)
Change in total costs	€ **-6,666 (-13,705; 1,595)**	€ **-5,256 (-7,479; -3,085)**	**€ 17,764 (5,456; 32,730)**	€ **-5,511 (-9,447; -1,484)**	**€ -6,473 (-11,017; -1,472)**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year.

Table 3.4: Results SA for scenario of one-unit change in a cohort aged 40 years old with BMI 35 kg/m² (UK), costs in 2020 euros (undiscounted).

Outcome	Base case	SA1: 20 years time horizon	SA2: RR BMI-diseases DYNAMO-HIA	SA3: RR BMI-all-cause mortality DYNAMO	SA4: no co-occurrence of diseases	SA5: including productivity costs	SA6: including productivity & non-medical costs
Assumptions that were changed:	-	20 years instead of lifetime	RRs from the DYNAMO-HIA (217,218) instead of GBD (216)	RRs from the DYNAMO-HIA (217,218) instead of Aune et al. (208)	No clustering of diseases assumed	Adding productivity costs	Adding productivity costs and non-medical costs
Gain in life expectancy (years)	0.657	0.032	0.614	0.567	0.533	0.657	0.657
Gain in QALY	0.598	0.053	0.553	0.534	0.489	0.598	0.598
Change in medical costs diabetes, IHD, stroke	€ -4,147	€ -1,024	€ -3,558	€ -4,254	€ -3,064	€ -4,147	€ -4,147
Change in medical costs for other diseases	€ 2,520	€42	€2,351	€2,151	€2,060	€ 2,520	€ 2,520
Change in non-medical costs	-	-	-	-	-	-	€ 7,368
Change in informal care costs	€1,086	-€16	€1022	€840	€906	€ 1,086	€ 1,086
Change in productivity costs	-	-	-	-	-	€ -52	€ -52
Change in total costs	**€ -539**	**€ -997**	**€ -185**	**€ -1,264**	**€ -97**	**€ -591**	**€6,777**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year; RR, relative risk; SA, sensitivity analysis.

The model validation exercises showed that in general, the current model resulted in slightly lower estimates of the life expectancy for both men and women compared with EUROSTAT data (i.e., 0.4-0.9 years lower compared with EUROSTAT data). See Appendix 3.5 for figures related to this validation check.

Comparison of the difference in life expectancy between a healthy and obese 40-year-old person with the current model and other published studies showed that results were comparable with the results presented by van Baal et al. (253) but lower than the results of Peeters et al. (252) The current model predicted a difference in life expectancy ranging from 3.7 years for the UK to 4.0 years for Spain comparable with the 4.2 years reported by van Baal et al. Peeters et al. reported a difference in life expectancy ranging from 5.82 to 6.85 years for men and from 6.18 to 7.21 years for women.

DISCUSSION

This study investigated the lifetime health and healthcare burden of obesity, by including a wide range of healthcare costs, in five European countries. We found that total lifetime costs and health outcomes varied between European countries; total costs were lowest in Greece and highest in the Netherlands. Annual treatment cost per case for obesity-related diseases obtained from the literature (Appendix 3.1: Table 3.1.3) showed substantial variation between countries, being the highest in Germany and the lowest in Greece. Medical costs for other diseases showed even larger variation. The latter costs were relatively low in Greece compared with other countries, because in Greece there is large out-of-pocket spending (i.e., private spending), which is not included in healthcare expenditure databases (244). Moreover, differences in medical costs for other diseases were calculated using best available data (244), using inpatient hospital care costs for Greece and multiple cost components for the Netherlands. In line with a previous study (204) health outcomes were better in a cohort with a BMI of 30 kg/m² compared with 35 kg/m², as higher BMI results in higher risks for obesity-related diseases.

In addition, we showed the potential of preventing obesity, by reducing high BMI with one unit and by assuming a reduction in BMI to a healthy BMI of 25 kg/m², resulting in gains in life expectancy and QALY. Moreover, the total healthcare costs will be reduced when obesity is prevented, which is comparable with other studies (200,254). However, in the Netherlands the total costs did not decrease because of a large increase in medical costs for other diseases. It must be noted that discount rates had not been applied in base case analyses; when discount rates were applied in the Netherlands, this resulted in cost savings for the Netherlands as well as the increase in medical costs for other diseases will happen in the future.

Applying a shorter time horizon is important for the final outcomes (SA1). In the analysis with a time horizon of 20 years, which is below the average life expectancy of a 40-year-old person with a BMI of 35 kg/m² (see Table 3.1; 38.6 years), the gain in life expectancy was very

low (0.032 years), resulting in only a small increase in medical costs for other diseases. The incremental informal care costs were negative, which could be explained by the fact that these costs mainly occur in the last year(s) of life (255). The results of SA6 did show a large impact of non-medical costs on the total lifetime costs and it could therefore be argued that these costs should not be neglected. There is still discussion in the literature whether to include these costs, but there is an increase in favor of the arguments as practical issues can be overcome (210,239,244,256).

One way to compare the burden of obesity in terms of reduced life expectancy with the additional health spending that might result of successful obesity prevention is to attach a monetary value to reduced life expectancy (257). Such monetary values are used in decision making based on cost effectiveness results. Monetary values that have been used in that context are defined, for example, by the National Institute for Health and Care Excellence (NICE) to be 20,000 pounds (22,676 euros) per 1 additional QALY (258). The scenario analyses on a population level showed a gain in QALY of 1.62 for preventing obesity, corresponding to a cost of €36,735 for reduced quality-adjusted life expectancy, which is much higher than the increase in healthcare costs (i.e., change in total costs) associated with obesity (about to €6,500 for the UK). Economic evaluations can help to assess whether specific interventions reducing BMI are good value for money by comparing the change in total lifetime costs with the acquired health benefits. It is important that new initiatives to prevent obesity keep being developed, such as the use of systems science for strategic planning of obesity, or by targeting a sustainable change in behavior by introducing personalized nutrition (23,259). Future studies can use this newly developed obesity model to evaluate the cost-effectiveness of obesity-related interventions.

The current study included a wide range of healthcare costs. Another strength of the study was that the newly developed Markov model is representative for five different countries, which allows comparison between countries on costs and health outcomes. In contrast to most previously published obesity models that include classes (e.g., normal weight, overweight and obese) (260), BMI was modeled continuously. Modeling BMI as a continuous parameter gives the model more flexibility in simulating the impact of, for example prevention, on BMI reductions. However, the model also had some limitations. First, only three main obesity-related diseases were modeled directly. Thus, the effect of BMI reduction on occurrence and costs of other obesity-related diseases could not be explicitly shown. A reduction in BMI has been shown to be beneficial for other diseases as well, such as osteoarthritis, sleep apnea, many types of cancers, and mental illness (261–263). The impact of these other diseases on life expectancy was considered, however, by including RRs for BMI on all-cause mortality. Costs for the other (obesity-related) diseases were included in the medical costs related to other diseases. Second, the model used BMI as a parameter to estimate the lifetime cost and effects of a certain cohort. However, other parameters, such as body fat or waist circumference, might yield more accurate estimates of the long-term costs and effects (194). The association between body fat and other factors such as life expectancy, QOL and costs, however, was

not yet well established in the literature. From the model validation, it could be found that results were slightly comparable or even somewhat conservative in comparison with other models. Finally, we did not consider any differences in BMI between ethnicities. However, it is shown that an equivalent risk of type 2 diabetes, was at substantially lower BMI values in black Caribbean, south Asian, Chinese, and Arab populations (in populations living in England) than the current BMI cut-offs for obesity (264). Future research could look at the impact of these ethnic differences on the total costs and effects.

In conclusion, our findings show that the total impact of obesity on healthcare costs is substantial in the five different countries that were investigated. In addition, results show that the life expectancy of people with obesity is on average about 4 years lower compared with people with a normal weight. Reductions in BMI resulted in a reduction of obesity-related diseases and a gain in life expectancy, which emphasizes the importance of reducing BMI and the development of interventions that support this reduction. However, the wide range of healthcare costs that was included showed that an increase in life expectancy, because of a BMI reduction, has implications for non-obesity-related healthcare costs, which is relevant to support decision making on implementation of preventive interventions.

APPENDICES

Appendix 3.1: Input data

Mean body mass index (BMI) in the population

The mean BMI by sex and 5-year age classes for the different countries was obtained from the Global Burden of Disease Study (216). To obtain estimates for the mean BMI in the general population by sex and one-year age classes, a generalized additive model with P-splines was estimated. The estimated model was used to predict the mean BMI values for the non-observed ages. The resulting mean BMI values by sex and age are shown in Figure 3.1.1.

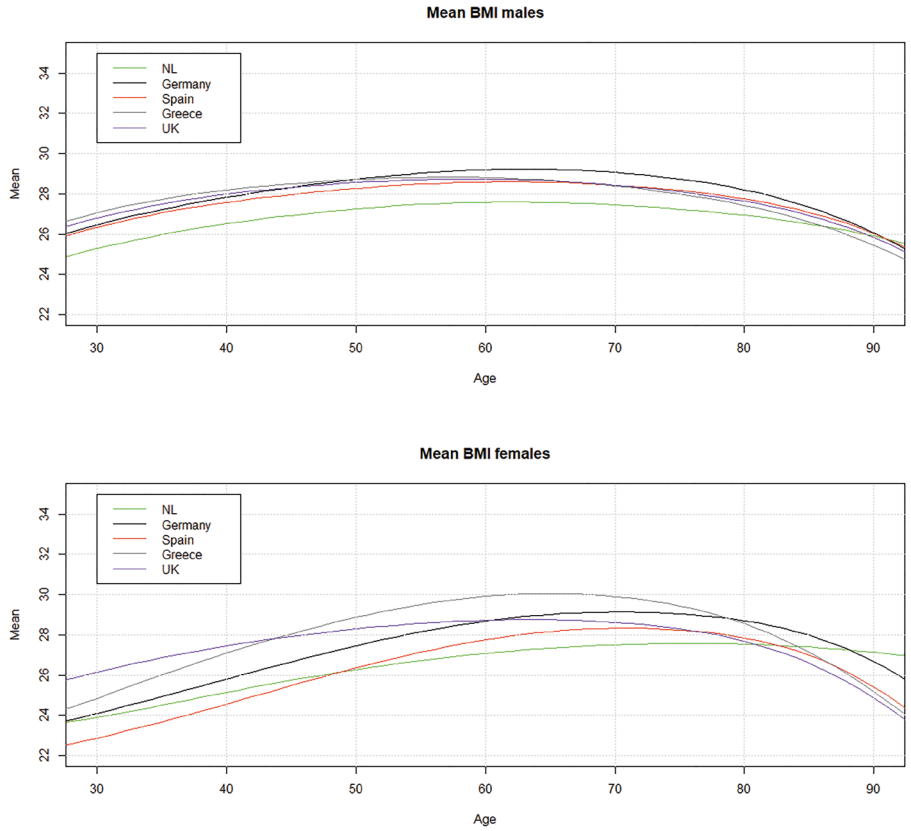


Figure 3.1.1: Mean BMI in the general population for a) males and b) females. Abbreviations: BMI, body mass index; NL, the Netherlands; UK, United Kingdom.

Association between BMI and all-cause mortality

Relative risks (RRs) for the association between BMI and all-cause mortality specified by sex were obtained from a meta-analysis of 230 cohort studies from Aune et al. (208). Based on the

RRs for all-cause mortality, reported for several BMI values in this meta-analysis, a function was estimated to describe the association between BMI and RR for all-cause mortality, which was done separately for males and females. Based on the reported data a generalized additive model with P-splines was estimated. The resulting association between BMI and all-cause mortality is shown in Figure 3.1.2.

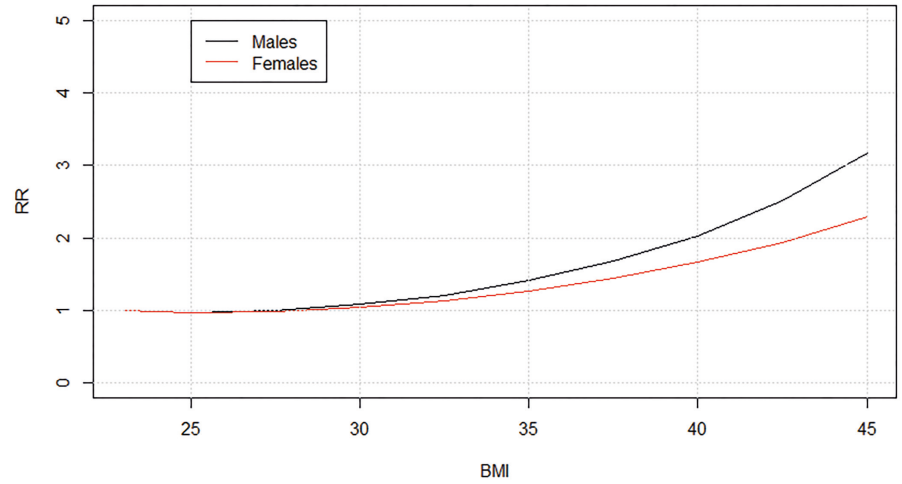


Figure 3.1.2: Association between BMI and relative risk for all-cause mortality. Abbreviations: BMI, body mass index; RR, relative risk.

Association between BMI and obesity-related diseases

RRs for the association between BMI and diabetes, IHD and stroke specified by age were obtained from the Global Burden of Disease study (216). Risks were expressed per 5-unit change in BMI. Risks were presented for different age classes, with decreasing risks for increasing ages. For stroke, the RRs for ischemic stroke were used. The RRs per 5-unit change in BMI were transformed to risks per 1-unit change in BMI. A generalized additive model with P-splines was estimated using the risks per 1-unit change in BMI. The estimated model was used to predict the RRs for the non-observed ages. The RRs outside the age range reported by the Global Burden of Disease study were assumed equal to the values reported for the first or last age class, respectively. RRs for 24 years of age and lower were assumed equal to the risks at age 25. RRs for age 86 and over were assumed equal to the risks at age 85. The resulting age-specific RRs shown in Figure 3.1.3.

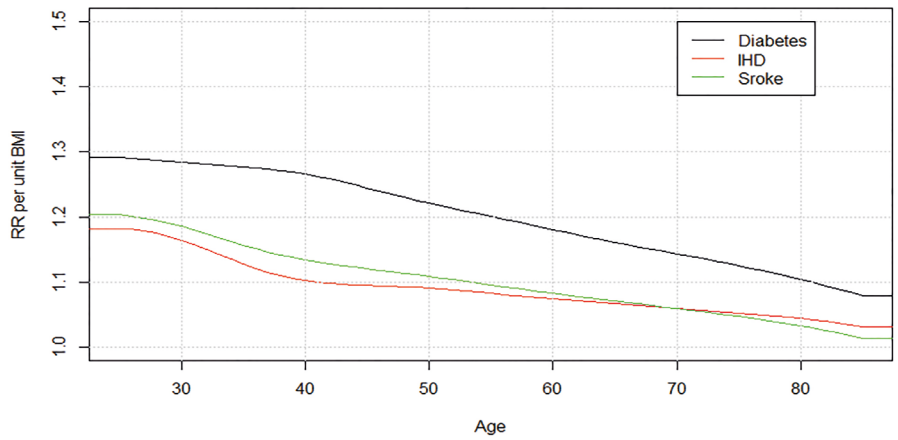


Figure 3.1.3: RRs for the association between BMI (one-unit change) and diabetes, IHD and stroke specified by age. Abbreviations: BMI, body mass index; IHD, ischemic heart disease; RR, relative risk.

Co-occurrence of obesity-related diseases

The DYNAMO-HIA study provided RRs for the co-occurrence of 'diabetes and stroke' and 'diabetes and IHD' (217,218). Risk for 'IHD and stroke' were not available but based on the paper of Van Baal et al. (219), these risks were assumed equal to the risks for 'diabetes and IHD'. See Table 3.1.1.

Table 3.1.1: Relative risk for co-occurrence of diseases.

Combination of diseases	Men	Women
Diabetes and IHD	2.66 (<age 55) 1.93 (>age 55)	3.53 (<age 65) 2.59 (>age 65)
Diabetes and stroke	2.0 (<age 50) 1.8 (>age 50)	2.9 (<age 50) 2.2 (>age 50)
IHD and stroke	Not available, assumed equal to diabetes and ischemic heart disease (219)	

Abbreviations: IHD, ischemic heart disease

Prevalence and incidence of obesity-related diseases

The prevalence, incidence, and excess mortality of diabetes, IHD and stroke specified by sex and age for the five European countries were obtained from the DYNAMO-HIA study (217,218). Reported data were specified by BMI using the following approach. In accordance with the meta-analysis of Aune et al. (208) a BMI of 23 was assumed to be the reference value with a RR of 1 for occurrence of obesity-related diseases. Using the RRs for the association between BMI and the disease, and the currently observed prevalence, incidence and BMI values for the general population, the disease prevalence and incidence at a RR of 1 were calculated using the following formulas:

$$Prev_{RR=1} = Prev_{observed} / RR\_disease^{(BMI-23)}$$

$$Inc_{RR=1} = Inc_{observed} / RR\_disease^{(BMI-23)}$$

Where $Prev_{RR=1}$ and $Inc_{RR=1}$ are the prevalence and incidence of the obesity-related disease for RR=1, $Prev_{observed}$ and $Inc_{observed}$ are the prevalence and incidence as observed in the general population and BMI is the BMI in the general population by sex and age. Based on $Prev_{RR=1}$ and $Inc_{RR=1}$ it is possible to calculate the prevalence and incidence of diseases for cohorts of people with a given BMI using the following formulas:

$$Prev_{cohort} = Prev_{RR=1} * RR\_disease^{(BMI\_cohort-23)}$$

$$Inc_{cohort} = Inc_{RR=1} * RR\_disease^{(BMI\_cohort-23)}$$

Where $Prev_{cohort}$ and Inc_{cohort} are the prevalence and incidence of the disease in the cohort of interest and BMI_cohort reflects the mean BMI value in the cohort.

Besides specifying prevalence and incidence of diabetes, IHD and stroke by BMI, the two parameters also needed to be divided over the different health states in the model. For the model, the parameters needed to be specified as prevalence and incidence from the healthy state as well as prevalence and incidence from disease states. The total prevalence and incidence observed in the population, is the combination of all different rates. For example, the incidence of diabetes observed in the population is the sum of the incidence of diabetes in healthy persons, in patients with IHD, in patients with stroke and in patients with both IHD and stroke. To make the incidence rates depending on the co-occurrence of other diseases, the approach as described below was used. First, the prevalence of the different combinations of diseases has been calculated using the following steps:

1. The prevalence rate of the combination of all three diseases has been calculated using the prevalence rates of the three diseases and the RRs for co-occurrence of the diseases:

$$Prev_{diabIHDstroke} = Prev_{diab} * Prev_{IHD} * Prev_{stroke} * RR_{diab\_IHD} * RR_{diab\_stroke}$$

2. The prevalence rate of the combinations of two diseases has been calculated as follows:

$$Prev_{diabIHD} = Prev_{diab} * Prev_{IHD} * RR_{diabIHD} - Prev_{diabIHDstroke}$$

$$Prev_{diabstroke} = Prev_{diab} * Prev_{stroke} * RR_{diabstroke} - Prev_{diabIHDstroke}$$

$$Prev_{IHDstroke} = Prev_{IHD} * Prev_{stroke} * RR_{strokeIHD} - Prev_{diabIHDstroke}$$

3. The prevalence rate of having one disease only has been calculated as follows:

$$Prev_{diab\_only} = Prev_{diab\_total} - Prev_{diabIHDstroke} - Prev_{diabIHD} - Prev_{diabstroke}$$

$$Prev_{IHD\_only} = Prev_{IHD\_total} - Prev_{diabIHDstroke} - Prev_{diabIHD} - Prev_{IHDstroke}$$

$$Prev_{stroke\_only} = Prev_{stroke\_total} - Prev_{diabIHDstroke} - Prev_{diabstroke} - Prev_{IHDstroke}$$

4. The population without diabetes, IHD or stroke has been calculated as:

$Pop_{healthy} = 1 - Prev_{diab\_only} - Prev_{IHD\_only} - Prev_{stroke\_only} - Prev_{diabIHD} - Prev_{diabstroke} - Prev_{IHDstroke} - Prev_{diabIHDstroke}$

Second, the total incidence of the three diseases has been divided over the different health states in the model using the total incidence rates of the three diseases, the prevalence rates of the different states as calculated above and the RRs for co-occurrence of the diseases.

Example diabetes:

$Inc\_diab_{healthy\_pop} = Inc_{diab\_total} / (Pop_{healthy} * 1 + Prev_{IHD\_only} * RR_{diabIHD} + Prev_{stroke\_only} * RR_{diabstroke} + Prev_{IHDstroke} * RR_{diabIHD} * RR_{diabstroke})$

$Inc\_diab_{IHD} = Inc\_diab_{healthy\_pop} * RR_{diabIHD}$

$Inc\_diab_{stroke} = Inc\_diab_{healthy\_pop} * RR_{diabstroke}$

$Inc\_diab_{IHDstroke} = Inc\_diab_{healthy\_pop} * RR_{diabstroke} * RR_{diabIHD}$

Figure 3.1.4-3.1.6 show the incidence rates of diabetes, IHD or stroke by sex, age, and BMI level in the UK as example.

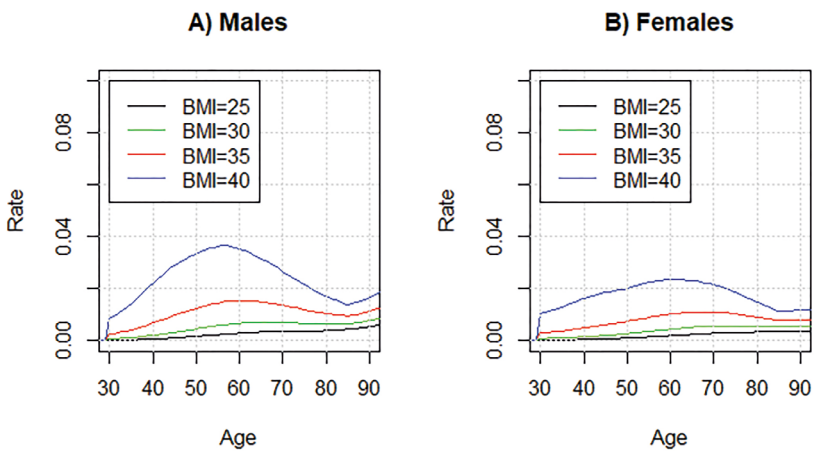


Figure 3.1.4: Incidence diabetes by sex, age, and BMI level (example UK). Abbreviations: BMI, body mass index.

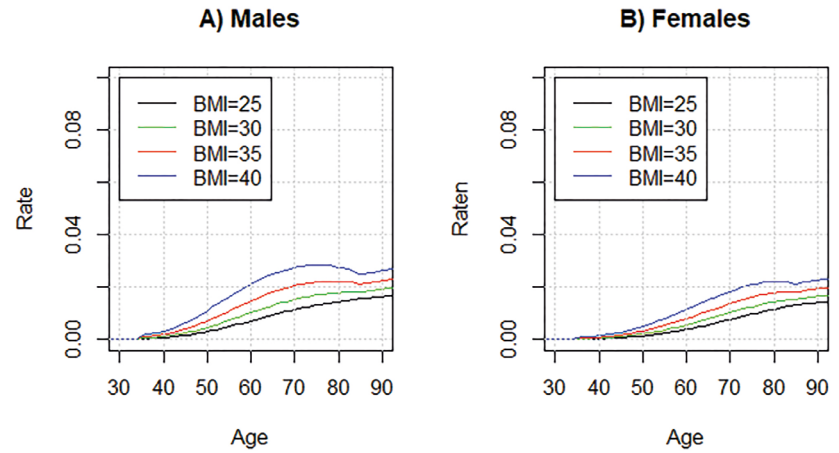


Figure 3.1.5: Incidence IHD by sex, age, and BMI level (example UK). Abbreviations: BMI, body mass index.

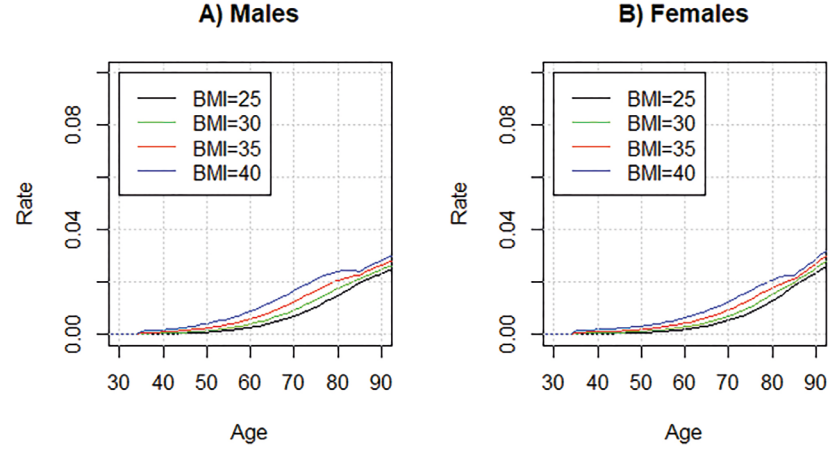


Figure 3.1.6: Incidence stroke by sex, age, and BMI level (example UK). Abbreviations: BMI, body mass index.

Mortality

All-cause mortality

All-cause mortality rates for the five different countries were calculated using the mortality numbers and population numbers in the different countries. A generalized additive model with p-splines assuming a Poisson distribution was estimated using the mortality numbers

as outcome, age as predictor and the logarithm of the population numbers as offset variable. The model was used to predict the all-cause mortality rates by sex and one-year age-classes (see Figure 3.1.7).

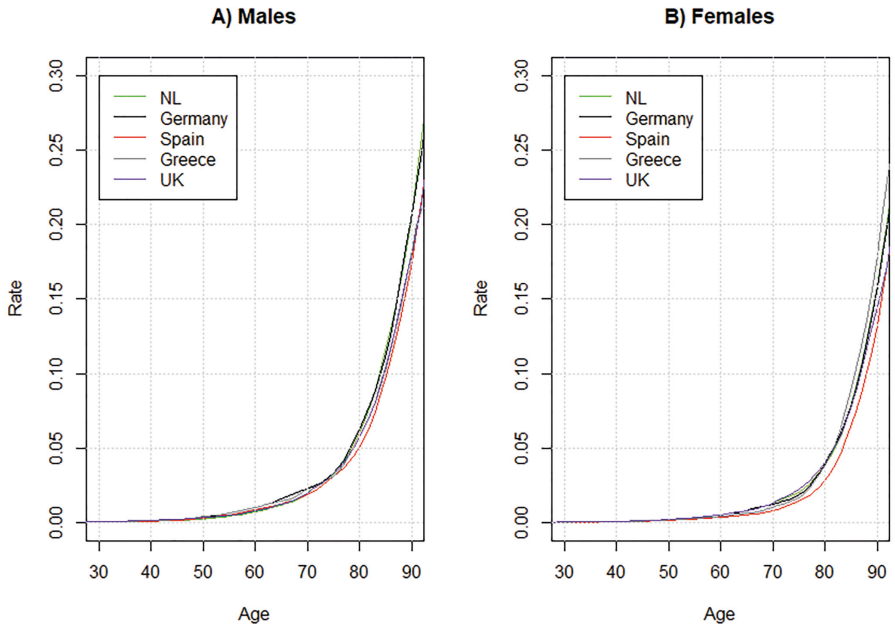


Figure 3.1.7: All-cause mortality rates for a) males and b) females. Abbreviations: NL, the Netherlands; UK, United Kingdom.

All-cause mortality rates were made dependent on BMI using the RRs for BMI and all-cause mortality and the currently observed BMI values for the general population. The all-cause mortality rate at a RR of 1 was calculated using the following formula:

$$Mort\_allcause_{\_RR=1} = Mort\_allcause_{\_obeserved} / RR\_allcause\_mortality\ (BMI_{\_population})$$

Based on $mort\_allcause_{\_RR=1}$ it is possible to calculate the all-cause mortality rate for a cohort of people with a given BMI using the following formulas:

$$Mort\_allcause_{\_cohort} = Mort\_allcause_{\_RR=1} * RR\_allcause\_mortality(BMI\_cohort)$$

Figure 3.1.8 shows the all-cause mortality rate for different BMIs.

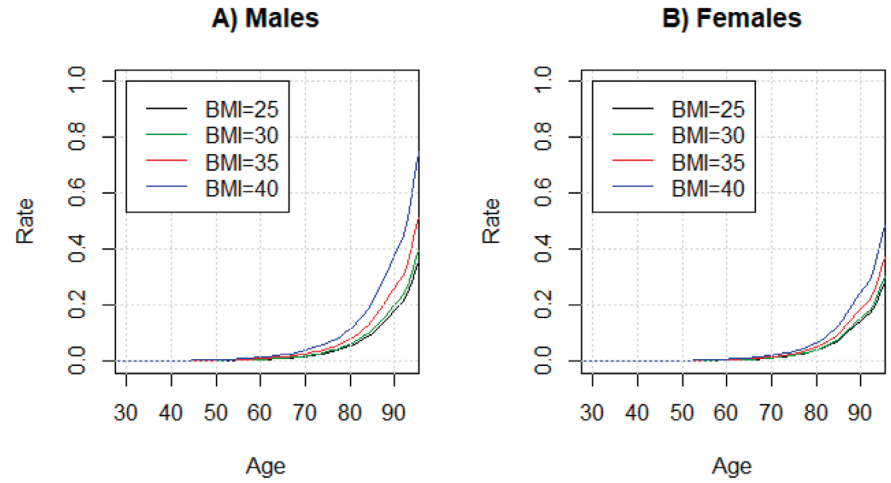


Figure 3.1.8: All-cause mortality by sex, age, and BMI level (example the UK). Abbreviations: BMI, body mass index.

Mortality for obesity-related diseases

Excess mortality is the additional mortality observed in a person with a specific disease compared to a person without the disease. The additional mortality is however, not all attributable to the disease itself. For example, the excess mortality in a person with diabetes is not only including mortality due to diabetes itself but also the increased risk that a person with diabetes dies from diseases with the same risk factors, for example cardiovascular disease. Excess mortality for diabetes, IHD and stroke in 2014 for the five European countries were obtained from the DYNAMO-HIA study (217,218). When a disease model includes multiple diseases, combining excess mortality data might lead to overestimation of the mortality for patients. The mortality of patients with two diseases is not simple the sum of the two excess mortality values, because as explained above the excess mortality for diabetes for example also includes increased mortality due to IHD, because diabetes patients have a higher risk for IHD as well. In a model with multiple diseases, the excess mortality therefore needs to be adjusted to attributable mortality figures, i.e., mortality due to the disease itself, to avoid double counting (222). The ratios between attributable mortality and excess mortality for diabetes, myocardial infarction and stroke were derived from a paper of Hoogenveen et al. (222) and applied to all country-specific estimates of excess mortality to derive the country-specific values for attributable mortality. The resulting attributable mortality rates are shown in Figure 3.1.9.

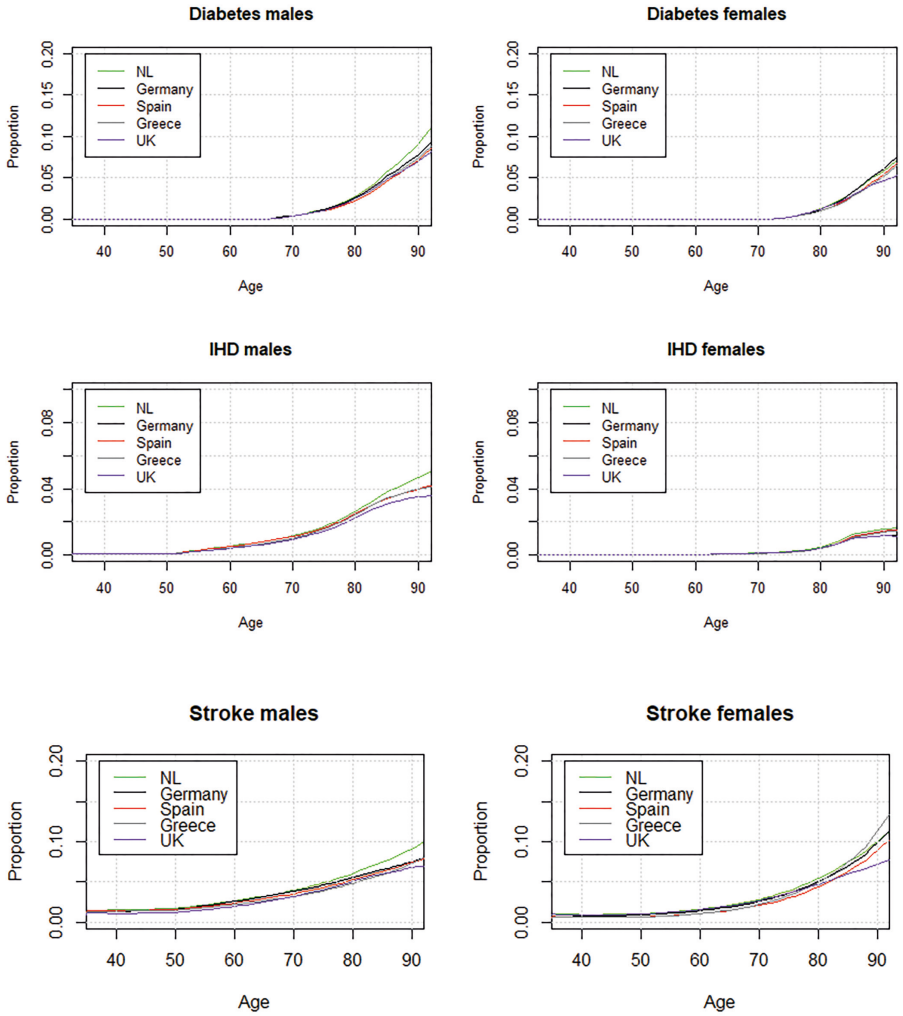


Figure 3.1.9: Attributable mortality rates for diabetes, IHD and stroke specified by sex. Abbreviations: IHD, ischemic heart disease; NL, the Netherlands; UK, United Kingdom.

Case-fatality rates

For both ischemic heart disease including myocardial infarction and stroke, which are events, a case-fatality rate has been applied. Because the model has a cycle length of one-year, case-fatality was defined as mortality within the first year after the event. The case-fatality rate was obtained from a Dutch study of Vaartjes et al. reporting the one-year risk of death after MI (220). Based on the age-specific case-fatality rates for myocardial infarction reported a log-linear model was estimated using the logarithm of the case-fatality rate as outcome and age as predictor. Based on the estimated model, the case-fatality rates for the unobserved ages

were calculated. Case-fatality rates outside the age range reported by Vaartjes et al. were set to a fixed value. The rate for age 51 and lower was set to the rate for the age of 52. The rate for age 89 and older was set to the rate of the age of 88. The case-fatality rate for stroke was obtained from a Dutch study of Vaartjes et al. presenting the one-year mortality rates after admission for stroke specified by sex and age (221). Based on these data a general additive model with P-splines was estimated. The model was used to predict the case-fatality rates in the unobserved ages. Case-fatality rates outside the age range reported by Vaartjes et al. were set to a fixed value. The rate for age 41 and lower was set to the rate for the age of 42. The rate for age 89 and older was set to the rate of the age of 88. The Dutch age-specific case fatality rates were adjusted to other countries using OECD data on the overall case-fatality for myocardial infarction and stroke for the other European countries (223,224). Resulting case-fatality rates are presented in Figure 3.1.10 and 3.1.11.

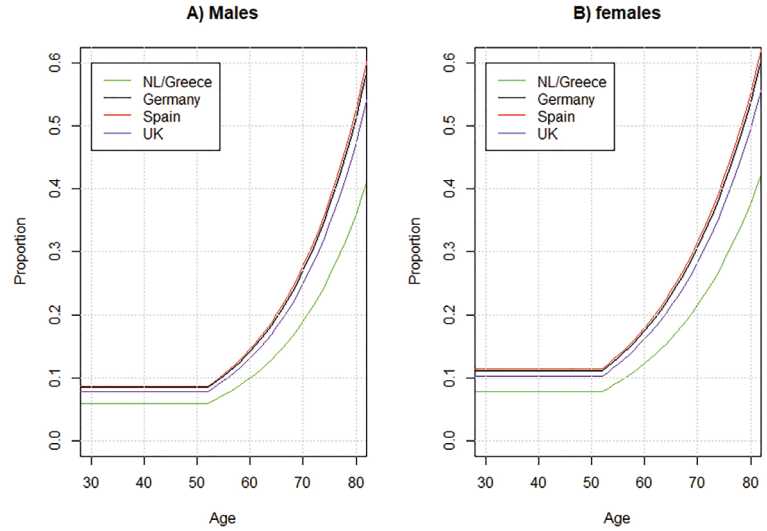


Figure 3.1.10: Case-fatality rate for IHD for a) males and b) females. Abbreviations: IHD, ischemic heart disease; NL, the Netherlands; UK, United Kingdom.

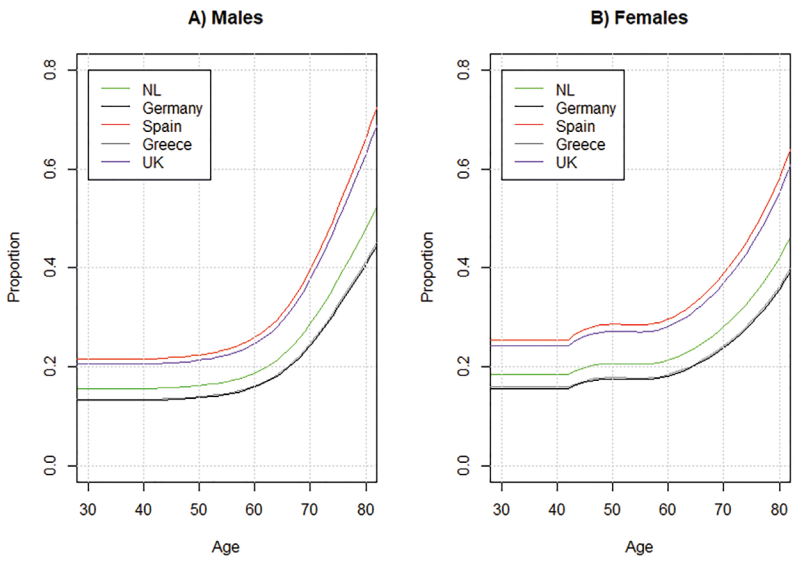


Figure 3.1.11: Case-fatality rate for stroke for a) males and b) females. Abbreviations: NL, the Netherlands; UK, United Kingdom.

Mortality due to other causes

The mortality due to other causes than diabetes, IHD and stroke was calculated using the all-cause mortality rates, the prevalence, incidence and attributable mortality rates for the three different diseases and the case-fatality rates for IHD and stroke.

Mort_othercauses = Mort_allcause - (Prev_diab * Mort_attrib_diab + Prev_IHD * Mort_attrib_IHD + Inc_IHD * Casefat_IHD + Prev_stroke * Mort_attrib_stroke + Inc_stroke * Casefat_stroke)

The mortality due to other causes for a specific cohort can be calculated using the following formula, where mortality for all-causes and prevalence and incidence for the different diseases are dependent on the BMI of the cohort:

$$Mort\_othercauses_{cohort} = Mort\_allcause_{cohort} - (Prev\_diab_{cohort} * Mort\_attrib\_diab + Prev\_IHD_{cohort} * Mort\_attrib\_IHD + Inc\_IHD_{cohort} * Casefat\_IHD + Prev\_stroke_{cohort} * Mort\_attrib\_stroke + Inc\_stroke_{cohort} * Casefat\_stroke)$$

Quality of life

Quality of life data were based on general population sex- and age-specific utilities based on the EQ-5D in the different countries (225), which were adjusted for the occurrence of diabetes, IHD and stroke using prevalence data and previously published utility decrements for the different diseases (226). Figure 3.1.12 shows the baseline utilities for the obesity model representing utilities for a population without diabetes, IHD and stroke.

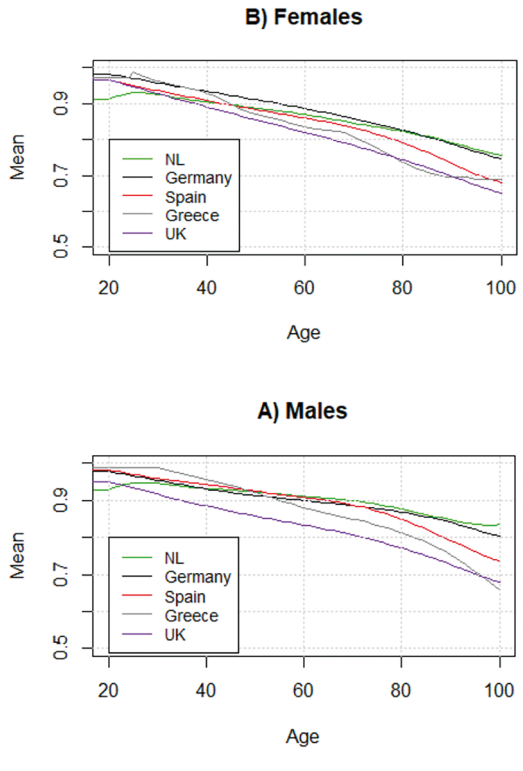


Figure 3.1.12: Baseline utilities for the obesity model representing utilities for a population without diabetes, IHD and stroke for a) males and b) females. Abbreviations: IHD, ischemic heart disease; NL, the Netherlands; UK, United Kingdom.

When diseases occur a decrement in the baseline utility is applied. Decrements are assumed to be additive. The country-specific utility decrements for diabetes, IHD and stroke are shown in Table 3.1.2.

Table 3.1.2: Utility decrements for obesity-related diseases for all five countries.

Disease	Germany	Greece	The Netherlands	Spain	United Kingdom
Diabetes	-0.0609	-0.0724	-0.0589	-0.0724	-0.0714
IHD	-0.0534	-0.0634	-0.0516	-0.0634	-0.0626
Stroke	-0.0998	-0.1187	-0.0966	-0.1187	-0.1171

Abbreviations: IHD, ischemic heart disease.

Costs

Cost of obesity-related diseases

Direct medical costs for treating diabetes, IHD and stroke were obtained from different literature sources (Table 3.1.3) (227–238). All costs were updated to 2020 euros.

Table 3.1.3: Annual costs for treating diabetes, IHD and stroke (price level 2020 euros).

Country	Diabetes	IHD†		Stroke	
		First year	Subsequent year	First year	Subsequent year
Germany	€1,696 (227)	€11,389 (228)	€5,735 (228)	€15,857 (228)	€10,901 (228)
Greece	€1,401 (229)	€6,159 (230)	€2,098 (230)	€4,523 (230)	€2,028 (230)
The Netherlands	€2,133 (231)	€5,687 (232)	€1,717 (233)	€16,174 (234)	€4,297 (234)
Spain	€1,449 (235)	€8,879 (236)	€5,260 (236)	€5,950 (236)	€2,209 (236)
United Kingdom	€1,782 (237)	€7,599 (238)	€4,814 (238)	€11,297 (238)	€5,941 (238)

†For IHD cost estimates for myocardial infarction were used. Abbreviations: IHD, ischemic heart disease.

Productivity costs

Hours of productivity loss were estimated based on the SHARE data (245) and specified for central-European countries (Germany, the Netherlands and the UK) and Southern-European countries (Spain and Greece). Costs for long-term work loss were calculated using data on the percentage of people with a paid job (Table 3.1.4), the mean number of working hours per week (Table 3.1.4) and the probability to become unemployed (Table 3.1.5) using the friction cost method (Table 3.1.6).

Table 3.1.4: Coefficient for the equation prediction probability to be employed at baseline†.

	Coefficients	
Country	**Central-European countries**	**Southern- European countries**
Intercept	-14.6526***	-11.8985***
Sex (female vs. male)	0.7523***	0.5874***
Age	-0.00861***	-0.00664***
Age²	-0.3354***	-0.5568***
Working hours per week	Males: 38, Females: 30	Males: 40, Females: 36

*** p<0.001; †Prob=exp(outcome_equation)/(1+exp(outcome_equation)).

Table 3.1.5: Coefficients for regression equation predicting the probability to become unemployed ‡.

Coefficient	Coefficients	
Country	**Central-European countries**	**Southern- European countries**
Intercept	-2.7395***	-2.7574***
Sex (Female=1)	0.09195**	0.2218***
Age (years, scaled) †	0.7042***	0.6529***
BMI (continuous)	0.01681***	0.01656**
Diabetes incidence (Yes=1)	-0.1404	0.05356
Stroke incidence (Yes=1)	0.2981*	0.3260
Heart attack incidence (Yes=1)	0.01624	-0.1029

† Age_scaled = as (age-mean[age])/std; where mean= =57.67046; std=6.064744
‡ Probability = exp(outcome_equation)/(1+exp(outcome_equation))
* significant at <0.05; **significant at <0.01; ***significant at <0.0001

In addition, productivity costs were calculated for short-term working hours lost estimated as the annual number of working days lost (Central-European countries: without disease = 10 days, with disease = 15 days, Southern-European countries: without disease = 7 days, with disease = 10 days).

Table 3.1.6: Friction period and reference prices for productivity across countries.

Country	Friction period in days	Productivity cost per hour 2020
Germany	69	€36,60
Greece	99	€16,90
Spain	75	€22,80
The Netherlands	85	€36,80
United Kingdom	82	€29,00

Cost for informal care

Costs for informal care were also based on the SHARE data and calculated using information on the percentage of people receiving informal care and the number of hours per day based on regression equations (Table 3.1.7 and 3.1.8). Both parameters were assumed to depend on sex, age, and time-to-death. Unit costs for informal care are shown in Table 3.1.9.

Table 3.1.7: Coefficients for the equation predicting weekly use of informal care (%) by European region†.

Parameter	Coefficients	
Country	**Central-European countries N=3,732**	**Southern- European countries N=3,282**
Intercept	-1.451***	-1.249**
Sex (female vs. male)	0.368**	0.286*
Age	0.054***	0.068***
Age²	0.0003	0.001*
Time-to-death (years)	-0.061***	-0.055**

* Significant at <0.05; **significant at <0.01; ***significant at <0.0001
† Probability = exp(outcome_equation)/(1+exp(outcome_equation))

Table 3.1.8: Coefficients for the equation predicting the use of informal care in hours per day†.

Parameter	Coefficients	
Country	**Central European countries N=549**	**Southern-European countries N=508**
Intercept	0.497**	1.449***
Sex (female vs. male)	0.112	0.053
Age	0.019***	0.005
Time-to-death (years)	-0.034**	-0.030*

* Significant at <0.05; **significant at <0.01; ***significant at <0.0001
† Number of hours = exp(outcome_equation)

Table 3.1.9: Reference prices for informal care.

Country	Reference price per hour (price 2020)
Germany	€12,60 (€13,00)
Greece	€7,30 (€7,40)
Spain	€10,90 (€11,20)
The Netherlands	€12,90 (€13,50)
United Kingdom	£13,11 (£20,30)

Medical costs for other diseases

Medical costs for other diseases were calculated as the total annual healthcare spending per capita (239–243,245) minus the related medical costs per capita, which were calculated by combining the direct medical costs per patient with the prevalence and incidence data for diabetes, IHD and stroke.

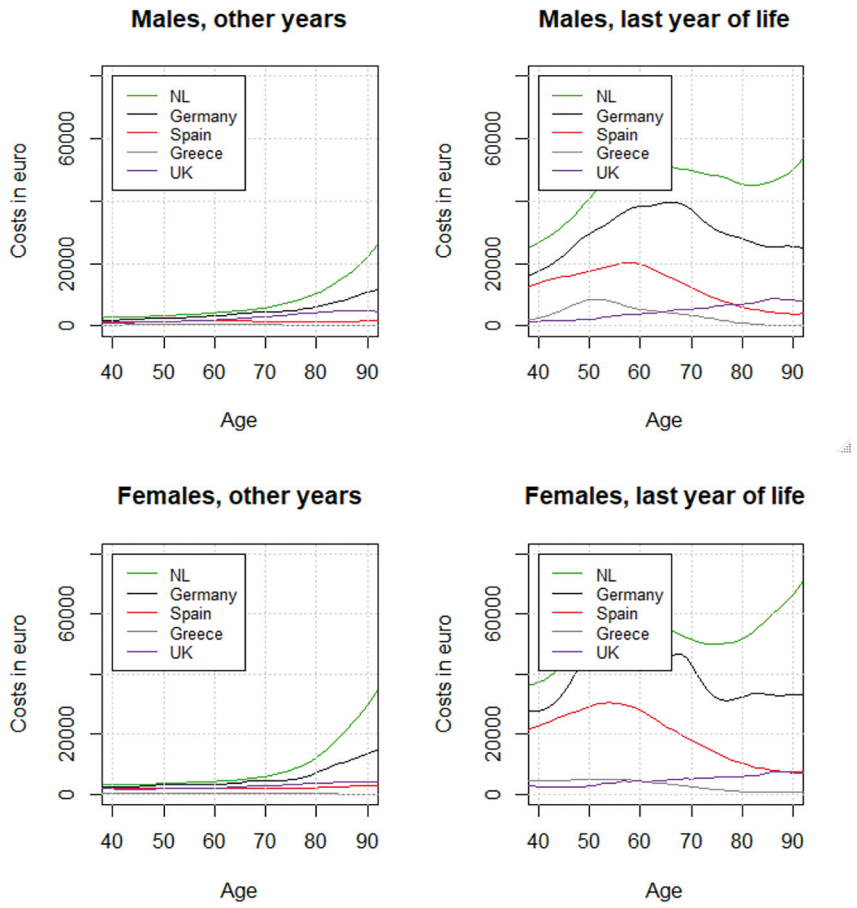


Figure 3.1.13: Medical costs for other diseases for males and females specified by last year of life and other years. Abbreviations: NL, the Netherlands; UK, United Kingdom.

Non-medical costs

Age-specific non-medical costs were estimated from national household consumption/ expenditure surveys in each country taking into account the household size (246–250) and presented in Figure 3.1.14.

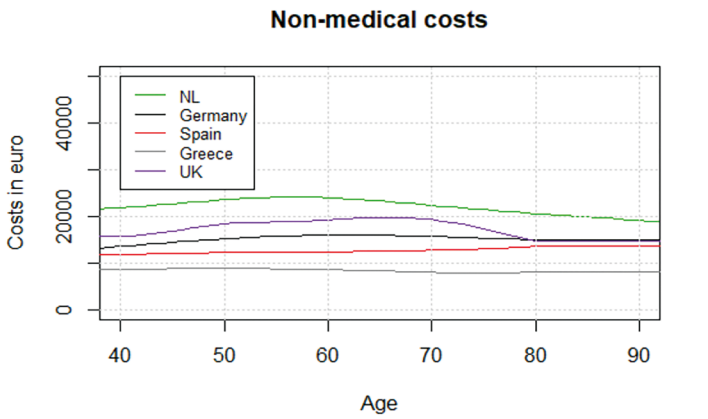


Figure 3.1.14: Non-medical costs by age. Abbreviations: NL, the Netherlands; UK, United Kingdom.

Appendix 3.2: Details probabilistic sensitivity analyses

To translate uncertainty around the input parameters into uncertainty around the outcomes of the model probabilistic sensitivity analysis (PSA) was performed. Uncertainty around the relative risks (RRs) for the association of BMI with all-cause mortality and the RRs for BMI and obesity-related diseases was included as well as uncertainty around costs. In addition, when the impact of a treatment reducing BMI is evaluated, uncertainty around effectiveness of the treatment and its costs is included. The other parameters were kept fixed.

Uncertainty around the RRs for the association of BMI and all-cause mortality was obtained from the publication of Aune et al. which reported uncertainty intervals around the RRs for 11 different BMI values (208). For each reported value of BMI 10 random values were drawn from the intervals around the RRs assuming a normal distribution. Based on the reported mean RRs and the surrounding uncertainty, a regression model with second degree polynomials was estimated, using RR as an outcome and BMI as predictor. For the PSA uncertainty was based on the uncertainty around the coefficients in the estimated model and random draws for all coefficients were made taking into account the co-variance of the coefficients. The regression model was estimated separately for males and females.

For the RRs reflecting the association between BMI and obesity-related diseases almost the same approach was used. The Global Burden of Disease Study reported the RRs for 12 different age groups including the uncertainty intervals. Again, 10 random draws around each observation were taken assuming a normal distribution. Afterwards a linear model was estimated based on the reported RRs and the surrounding uncertainty using relative risk as outcome and age as predictor. For the PSA random draws for the coefficients were made taking into account the co-variance.

Uncertainty around costs was not available. Therefore, a SE of 20% of the mean value was assumed for all cost estimates. For costs a gamma distribution was assumed. Uncertainty around the effectiveness and medical costs of reducing BMI was assumed to following a normal distribution.

Appendix 3.3: Discounted results

Table 3.3.1: Lifetime results (per person) for the base-case analysis for a healthy cohort (starting age of 40 years) and different BMI levels in the absence of any weight loss intervention, costs in 2020 euros.*

BMI	Outcome	Germany	Greece	Netherlands	Spain	United Kingdom
30 kg/ m2	**Life expectancy (years)**	22.7	22.8	29.9	23.2	21.0
	Years with diabetes	2.2	1.7	4.0	3.0	1.2
	Cum. Incident cases IHD /1000**	331	194	375	204	338
	Cum. Incident cases stroke /1000**	280	557	294	288	317
	QALY	20.081	19.597	26.074	20.247	17.369
	Medical costs diabetes, IHD, stroke	€ 22,235	€ 8,325	€ 10,405	€ 11,506	€ 13,785
	Medical costs for other diseases	€ 90,718	€ 9,896	€ 101,153	€ 45,786	€ 45,557
	Informal care costs	€ 5,338	€ 9,156	€ 3,851	€ 14,390	€ 7,912
	Total costs	**€ 118,291**	**€ 27,376**	**€ 115,409**	**€ 71,682**	**€ 67,254**
35 kg/ m2	**Life expectancy (years)**	21.8	22.0	28.4	22.4	20.3
	Years with diabetes	5.0	3.6	8.1	6.1	2.7
	Cum. Incident cases IHD /1000	418	246	463	275	406
	Cum. Incident cases stroke /1000	354	604	382	365	382
	QALY	19.081	18.714	24.426	19.239	16.648
	Medical costs diabetes, IHD, stroke	€ 35,546	€ 13,092	€ 18,525	€ 19,820	€ 21,258
	Medical costs for other diseases	€ 85,878	€ 9,814	€ 95,193	€ 44,754	€ 43,163
	Informal care costs	€ 4,878	€ 8,442	€ 3,608	€ 13,235	€ 7,341
	Total costs	**€ 126,303**	**€ 31,348**	**€ 117,326**	**€ 77,808**	**€ 71,760**

*Discount rates: Germany; costs 3% effects 3%, Greece; costs 3% effects 3%, the Netherlands; costs 4% effects 1.5%, Spain; costs 3% effects 3%, United Kingdom; costs 3.5% effects 3.5%.
**No discounting applied.

Table 3.3.2: Lifetime results (per person) for the base-case analysis of one unit decrease in BMI for a cohort age 40 years, costs in 2020 euros.*

BMI	Outcome	Germany	Greece	Netherlands	Spain	United Kingdom
30 kg/m2	**Gain in life expectancy (years)**	0.112	0.109	0.201	0.111	0.088
	Decrease in years with diabetes	0.349	0.247	0.563	0.427	0.187
	Decrease in cum. Incident cases IHD /1000**	15	9	16	12	13
	Decrease in cum. Incident cases stroke /1000**	12	11	15	13	12
	Gain in QALY	0.127	0.116	0.221	0.132	0.091
	Change in medical costs diabetes, IHD, stroke	€ -1,891	€ -694	€ -1,111	€ -1,170	€ -1,096
	Change in medical costs for other diseases	€ 665	€ 11	€ 868	€ 141	€ 304
	Change in informal care costs	€ 63	€ 98	€ 34	€ 159	€ 77
	Change in total costs	**€ -1,162**	**€ -586**	**€ -208**	**€ -870**	**€ -715**
35 kg/m2	**Gain in life expectancy (years)**	0.224	0.210	0.371	0.215	0.180
	Decrease in years with diabetes	0.701	0.470	0.983	0.769	0.391
	Decrease in cum. Incident cases IHD /1000**	19	11	18	16	14
	Decrease in cum. Incident cases stroke /1000**	17	8	20	17	14
	Gain in QALY	0.252	0.22	0.403	0.251	0.183
	Change in medical costs diabetes, IHD, stroke	€ -3,273	€ -1,155	€ -2,018	€ -2,031	€ -1,815
	Change in medical costs for other diseases	€ 1,148	€ 20	€ 1,366	€ 247	€ 598
	Change in informal care costs	€ 109	€ 170	€ 57	€ 275	€ 137
	Change in total costs	**€ -2,015**	**€ -966**	**€ -594**	**€ -1,510**	**€ -1,081**

*Discount rates: Germany: costs 3% effects 3%, Greece; costs 3% effects 3%, the Netherlands; costs 4% effects 1.5%, Spain; costs 3% effects 3%, United Kingdom; costs 3.5% effects 3.5%.
**No discounting applied.

Appendix 3.4: Results sensitivity analyses for scenario of one-unit change in a cohort aged 40 years old with BMI 35 kg/m2

Table 3.4.1: Results for Germany.

Outcome	Base case	SA1: 20 years time horizon	SA2: RR BMI-diseases DYNAMO-HIA	SA3: RR BMI-all-cause mortality DYNAMO	SA4: no co-occurrence of diseases	SA5: including productivity costs	SA6: including productivity & non-medical costs
Assumptions that were changed:	-	20 years instead of lifetime	RRs from the DYNAMO-HIA (217,218) instead of GBD (216)	RRs from the DYNAMO-HIA (217,218) instead of Aune et al. (208)	No clustering of diseases assumed	Adding productivity costs	Adding productivity costs and non-medical costs
Gain in life expectancy (years)	0.675	0.032	0.614	0.601	0.526	0.675	0.675
Gain in QALY	0.692	0.045	0.621	0.633	0.548	0.692	0.692
Change in medical costs diabetes, IHD, stroke	€ -6,744	€ -1,702	€ -5,418	€ -6,916	€ -4,178	€ -6,744	€ -6,744
Change in medical costs for other diseases	€ 4,735	€ -78	€ 4,312	€ 3,974	€ 3,808	€ 4,735	€ 4,735
Change in non-medical costs	-	-	-	-	-	-	€ 10,148
Change in informal care costs	€ 610	€ -11	€ 555	€ 502	€ 487	€ 610	€ 610
Change in productivity costs	-	-	-	-	-	€ -87	€ -87
Change in total costs	**€ 1,398**	**€ -1,791**	**€ -550**	**€ -2,441**	**€ 117**	**€ -1,486**	**€ 8,662**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year; RR, relative risk; SA, sensitivity analysis.

Table 3.4.2: Results for Greece.

Outcome	Base case	SA1: 20 years time horizon	SA2: RR BMI-diseases DYNAMO-HIA	SA3: RR BMI-all-cause mortality DYNAMO	SA4: no co-occurrence of diseases	SA5: including productivity costs	SA6: including productivity & non-medical costs
Assumptions that were changed:	-	20 years instead of lifetime	RRs from the DYNAMO-HIA (217,218) instead of GBD (216)	RRs from the DYNAMO-HIA (217,218) instead of Aune et al. (208)	No clustering of diseases assumed	Adding productivity costs	Adding productivity costs and non-medical costs
Gain in life expectancy (years)	0.645	0.03	0.614	0.561	0.527	0.645	0.645
Gain in QALY	0.611	0.053	0.566	0.554	0.503	0.611	0.611
Change in medical costs diabetes, IHD, stroke	€ -2,369	€ -577	€ -2,168	€ -2,434	€ -1,889	€ -2,369	€ -2,369
Change in medical costs for other diseases	€ 91	€ -11	€ 86	€ 80	€ 76	€ 91	€ 91
Change in non-medical costs	-	-	-	-	-	-	€ 5,072
Change in informal care costs	€ 946	€ -14	€ 880	€ 754	€ 783	€ 946	€ 946
Change in productivity costs	-	-	-	-	-	-€ 59	-€ 59
Change in total costs	**€ -1,332**	**€ -603**	**€ -1,201**	**€ -1,600**	**€ -1,030**	**€ -1,391**	**€ 3,681**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year; RR, relative risk; SA, sensitivity analysis.

Table 3.4.3: Results for the Netherlands.

Outcome	Base case	SA1: 20 years time horizon	SA2: RR BMI-diseases DYNAMO-HIA	SA3: RR BMI-all-cause mortality DYNAMO	SA4: no co-occurrence of diseases	SA5: including productivity costs	SA6: including productivity & non-medical costs
Assumptions that were changed:	-	20 years instead of lifetime	RRs from the DYNAMO-HIA (217,218) instead of GBD (216)	RRs from the DYNAMO-HIA (217,218) instead of Aune et al. (208)	No clustering of diseases assumed	Adding productivity costs	Adding productivity costs and non-medical costs
Gain in life expectancy (years)	0.653	0.027	0.582	0.583	0.498	0.653	0.653
Gain in QALY	0.681	0.062	0.601	0.621	0.527	0.681	0.681
Change in medical costs diabetes, IHD, stroke	€ -4,914	€ -1,489	€ -4,195	€ -4,941	€ -3,952	€ -4,914	€ -4,914
Change in medical costs for other diseases	€ 9,129	€ -96	€ 8,107	€ 7,453	€ 7,314	€ 9,129	€ 9,129
Change in non-medical costs	-	-	-	-	-	-	€ 6,677
Change in informal care costs	€ 617	€ -10	€ 546	€ 505	€ 484	€ 617	€ 617
Change in productivity costs	-	-	-	-	-	-€ 101	-€ 101
Change in total costs	**€ 4,832**	**€ -1,596**	**€ 4,458**	**€ 3,016**	**€ 3,846**	**€ 4,731**	**€ 11,408**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year; RR, relative risk; SA, sensitivity analysis.

Table 3.4.4: Results for Spain.

Outcome	Base case	SA1: 20 years time horizon	SA2: RR BMI-diseases DYNAMO-HIA	SA3: RR BMI-all-cause mortality DYNAMO	SA4: no co-occurrence of diseases	SA5: including productivity costs	SA6: including productivity & non-medical costs
Assumptions that were changed:	-	20 years instead of lifetime	RRs from the DYNAMO-HIA (217,218) instead of GBD (216)	RRs from the DYNAMO-HIA (217,218) instead of Aune et al. (208)	No clustering of diseases assumed	Adding productivity costs	Adding productivity costs and non-medical costs
Gain in life expectancy (years)	0.677	0.027	0.608	0.6	0.514	0.677	0.677
Gain in QALY	0.696	0.068	0.623	0.639	0.55	0.696	0.696
Change in medical costs diabetes, IHD, stroke	€ -4,207	€ -1,115	€ -3,837	€ -4,221	€ -3,240	€ -4,207	€ -4,207
Change in medical costs for other diseases	€ 1,073	€ -41	€ 959	€ 893	€ 822	€ 1,073	€ 1,073
Change in non-medical costs	-	-	-	-	-	-	€ 8,745
Change in informal care costs	€ 1,573	€ -20	€ 1,409	€ 1,296	€ 1,225	€ 1,573	€ 1,573
Change in productivity costs	-	-	-	-	-	€ -49	€ -49
Change in total costs	**€ -1,563**	**€ -1,176**	**€ -1,470**	**€ -2,032**	**€ -1,192**	**€ -1,612**	**€ 7,133**

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; kg, kilograms; m, meter; QALY, quality-adjusted life year; RR, relative risk; SA, sensitivity analysis.

Appendix 3.5: Validation check 1

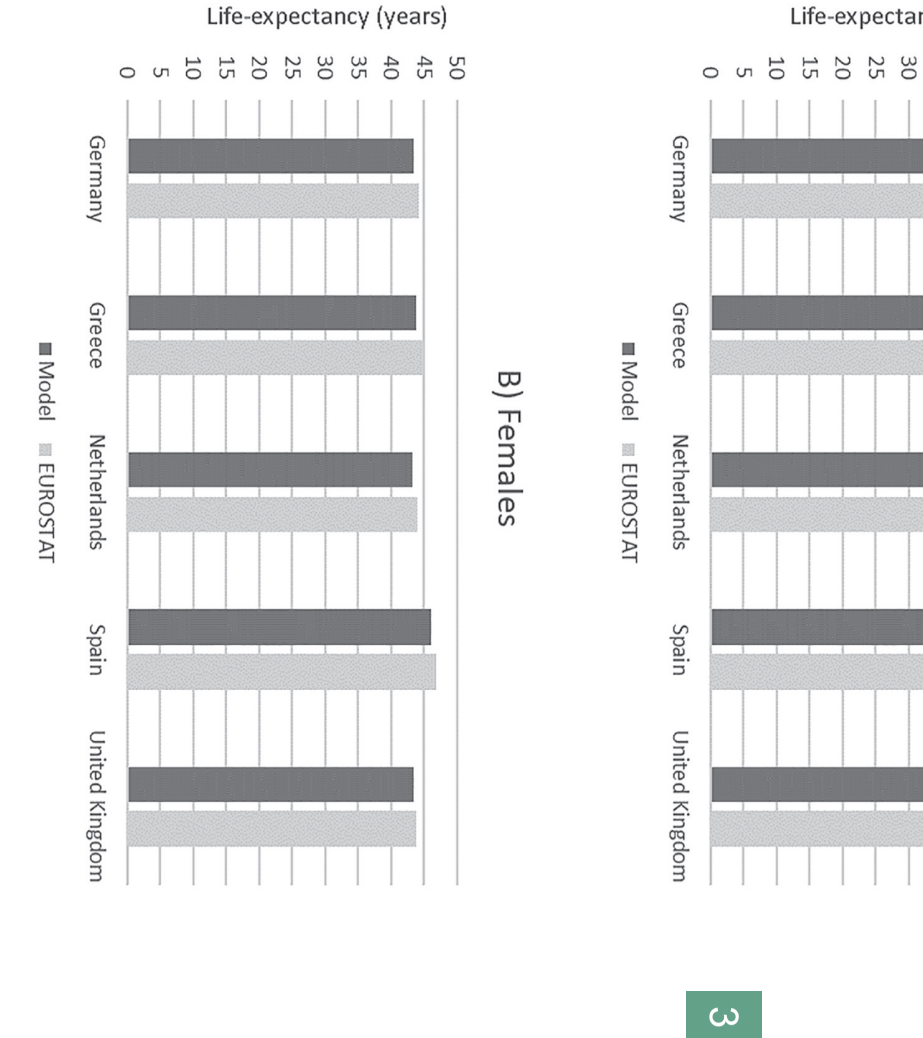
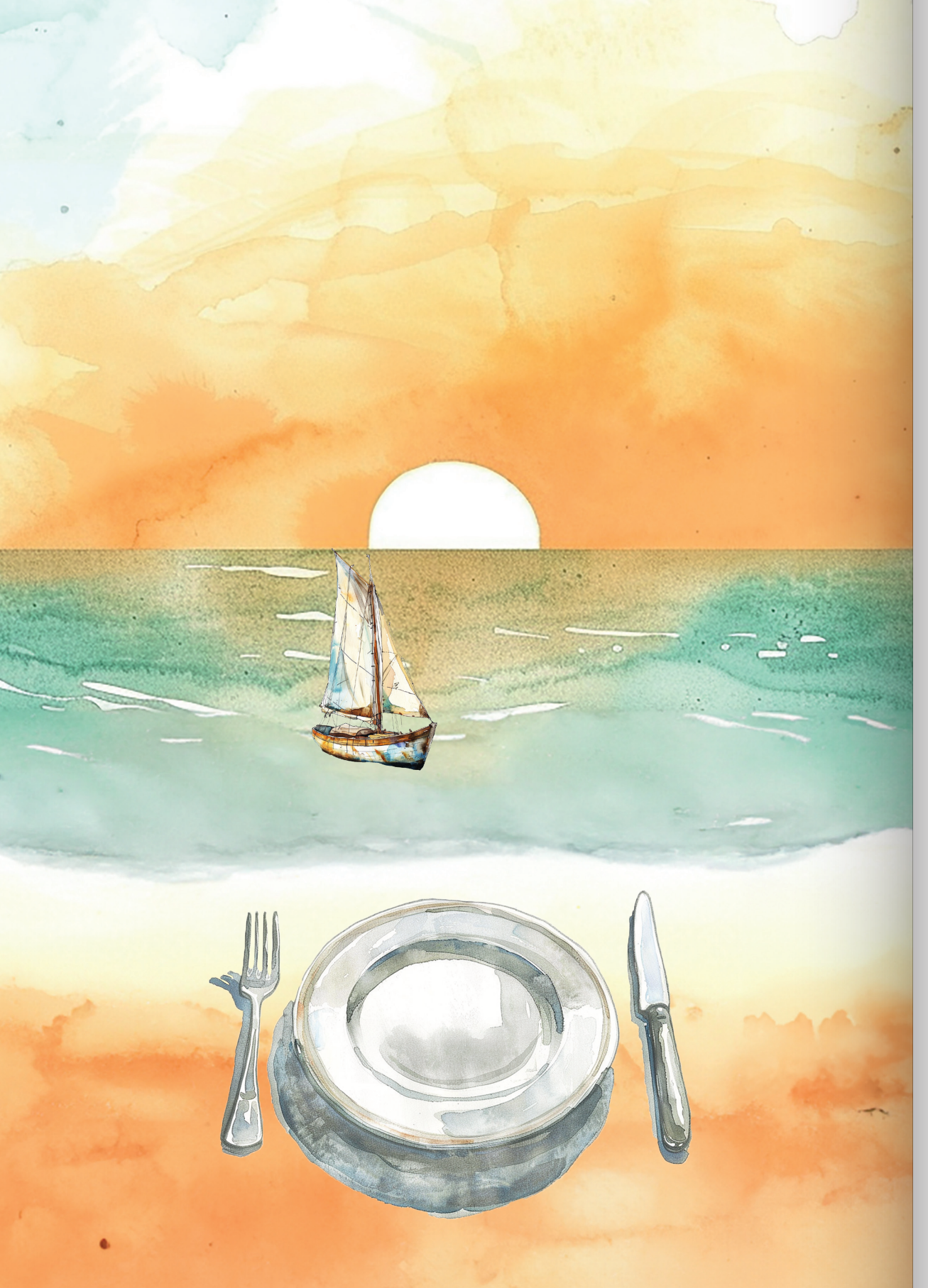


Figure 3.5.1: Validation of predicted life expectancy for a 40-year-old in the general population for A) males and B) females.

Part 2

Competitions: conducting cost-effectiveness analyses



Chapter 4

Economic evaluation of a personalized nutrition plan based on omic sciences versus a general nutrition plan in adults with overweight and obesity: a modeling study based on trial data in Denmark

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PharmacoEconomics-Open. 2023; 8(2): 313-331.

ABSTRACT

Objectives

Since there is no diet that is perfect for everyone, personalized nutrition approaches are gaining popularity to achieve goals such as the prevention of obesity-related diseases. However, appropriate choices about funding and encouraging personalized nutrition approaches should be based on sufficient evidence of their effectiveness and cost-effectiveness. In this study, we assessed whether a newly developed personalized plan (PP) could be cost-effective relative to a non-personalized plan in Denmark.

Methods

Results of a 10-week randomized controlled trial were combined with a validated obesity economic model to estimate lifetime cost-effectiveness. In the trial, the intervention group (PP) received personalized home-delivered meals based on metabolic biomarkers and personalized behavioral change messages. In the control group these meals and messages were not personalized. Effects were measured in body mass index (BMI) and quality of life (EQ-5D-5L). Costs [euros (€),2020] were considered from a societal perspective. Lifetime cost-effectiveness was assessed using a multi-state Markov model. Univariate, probabilistic sensitivity, and scenario analyses were performed.

Results

In the trial, no significant differences were found in the effectiveness of PP compared with control, but wide confidence intervals (CIs) were seen [e.g., BMI (-0.07, 95% CI: -0.51, 0.38)]. Lifetime estimates showed that PP increased costs (€520,102 versus €518,366, difference: €1,736) and quality-adjusted life years (QALYs) (15.117 versus 15.106, difference: 0.011); the incremental cost-utility ratio (ICUR) was therefore high (€158,798 to gain one QALY). However, a 20% decrease in intervention costs would reduce the ICUR (€23,668 per QALY gained) below an unofficial gross domestic product (GDP)-based willingness to pay threshold (€47,817 per QALY gained).

Conclusions

On the basis of the willingness to pay threshold and the non-significant differences in short-term effectiveness, PP may not be cost-effective. However, scaling up the intervention would reduce the intervention costs. Future studies should be larger and/or longer to reduce uncertainty about short-term effectiveness.

INTRODUCTION

Overweight [body mass index (BMI) ≥ 25 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) are growing public health problems (194). Globally, the prevalence of obesity has nearly tripled between 1975 and 2016 (194). Moreover, research from the Organization for Economic Cooperation and Development (OECD) shows that the average rates of adult obesity in OECD countries has risen from 21.3% in 2010 to 24.0% in 2016; this corresponds to an additional 50 million people with obesity (11). Additionally, in 34 out of 36 OECD member countries, more than half of the population is now overweight (11). A higher BMI is in turn a major risk factor for non-communicable diseases, such as cardiovascular diseases (the leading cause of death in 2012), diabetes, musculoskeletal disorders, and some cancers (194). These diseases and obesity itself will reduce the average life expectancy by 2.7 years across OECD countries over the period 2020–2050 (11). Because of these related diseases and the direct negative effect of overweight and obesity on physical ability and mental health (e.g., stress, depression, and anxiety) (265–267), people may be hampered in their capacity to perform their daily activities. Altogether, these negative physical and mental conditions reduce health-related quality of life (HRQoL) (268,269). Fortunately, studies have shown that weight loss is associated with improved HRQoL (269–271).

In addition to the huge global health problems caused by overweight and obesity, these conditions also pose a serious threat to the economy (11). On average, 8.4% of the health budget of OECD countries is spent on treating the consequences of obesity (11,201). In the USA this number is even higher, at 14% of the health budget (11). Besides healthcare costs, obesity has a rising impact on other social costs as well, such as patient and family costs and productivity losses (272,273). Lifetime productivity losses are almost twice as high in the obesity population compared with normal weight populations (272).

A well-balanced healthy diet is one of the key factors to prevent overweight, obesity, and related diseases (11). Several studies showed relationships between dietary patterns and significant changes in BMI over time (274–276). Countries have therefore implemented different policies to tackle overweight and obesity, including those targeting diets (11). However, obesity is a complex multifactorial disorder, which makes its management a challenging task (277). One single ‘perfect’ diet suitable for everyone may not exist because of the interindividual variation in a dietary treatment response (i.e., how the body utilizes and metabolizes nutrients), due to multiple phenotypic factors and genetic variants (173,278,279). Therefore, there is an increasing demand for studies investigating personalized nutrition approaches, rather than approaches on a population level (23). Personalized nutrition could be defined as “an approach that uses information on individual characteristics to develop targeted nutritional advice, products or services” (23). Several studies have already proven the effectiveness of personalized nutrition, but they have not yielded consistent findings (36,37). For example, the Food4Me study did not find significant gene-diet interaction effects on body weight but did find more appropriate changes in dietary behavior in a personalized nutrition

group versus a control group (a non-personalized intervention) (38). Moreover, Zeevi et al. (24) showed that personalized diets created with an accurate predictor of blood glucose response, considering dietary habits, physical activity, and gut microbiota, may successfully modify elevated postprandial blood glucose and its metabolic consequences.

Although there is a growing interest in advanced omics technologies to facilitate holistic approaches to biological problems (e.g., metabolomics, transcriptomics, and genomics), there is a need for a simple, effective, and affordable personalized nutrition tool that integrates these technologies with other nutritional and psychological aspects (8). To address this need, the PREVENTOMICS project (Horizon 2020: no. 818318) took an innovative approach by integrating genetic, nutritional, and psychological sciences with state-of-the-art metabolomics technologies and computational modeling. The outcome of this project was a comprehensive platform that includes a decision support system (DSS) (8,46). This platform effectively combines genetic, nutritional, biochemical, physiological, and behavioral factors and utilizes machine learning techniques to provide personalized dietary recommendations [24,25]. This study reports the results of the Danish intervention, in which the platform is integrated in an e-commerce digital tool created for delivering personalized meals plus a behavioral change program (i.e., personalized plan, PP) to sustainably improve the health status of people with overweight or obesity and thereby prevent obesity-related diseases (46). Effectiveness results showed that the PP intervention did not significantly improve health measures beyond those produced by the control (non-personalized) intervention (47). However, the wide confidence intervals (CIs) around the effectiveness estimates (e.g., effect in BMI of PP versus control: -0.07, 95% CI -0.51, 0.38) shows that the PP nutrition may still be more effective than a non-personalized intervention.

In addition to activities to assess the evidence regarding the effectiveness of personalized nutrition interventions, it is important to assess the cost-effectiveness of these interventions since policymakers expect evidence of cost-effectiveness when making reimbursement decisions. There is still a lack of cost-effectiveness literature relating to newly developed personalized nutrition interventions that specifically focus on omics-based personalized nutrition (280). This is, however, especially crucial to evaluate, given the potentially higher estimated costs of using omics technologies to personalize interventions (48). An economic evaluation can help to shed light on whether this intervention might potentially be cost-effective. Such information is especially important at this stage of first integration of the intervention, as it can help to inform developers of personalized nutrition interventions, as well as possible payers of the interventions. The aim of this study is therefore to evaluate the potential cost effectiveness of the PP intervention versus a control intervention (non-personalized) in adults with overweight and obesity in Denmark.

METHODOLOGY

Overall study design

Results regarding clinical and health outcomes from a clinical trial in Denmark (i.e., short-term results) (registered at clinicaltrial.gov (NCT04590989) were analyzed and then used to estimate the long-term effects, costs, and cost-effectiveness of the PP intervention versus control, using a validated obesity cost-effectiveness model (281). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was followed (282).

Study population

The study population included in these analyses, was based on the population included in the Danish trial within the PREVENTOMICS project. Participants in this intervention were women and men aged 18–65 years with overweight or obesity (BMI of 27 kg/m^2 but < 40 kg/m^2) and had no chronic diseases (e.g., diabetes and cancer) (46,47).

Trial description

The Danish trial was a 10-week randomized, single-center, parallel-group, double-blinded intervention study (46,47). The study had two intervention arms: PP and control. Participants were allocated in a 1:1 ratio, that was stratified by five 'clusters', to either PP or control. The clusters involved were oxidative stress, inflammation, carbohydrate metabolism, lipid metabolism and microbiota-generated metabolites (8). Information into which cluster to classify the participant, was gathered from a metabolome analysis of 51 biomarkers quantified from urine, plasma, and serum samples taken during the pre-baseline visit. Moreover, saliva analysis of 35 different single nucleotide polymorphisms was used, since they could affect the biomarker levels associated with the five clusters (46,47). Together, the biomarkers and saliva analysis provided a score for each cluster. This was done by using proprietary algorithms for any participant where both the absolute value of the biomarker in the biofluid and the biological relevance of the biomarker in the metabolic cluster were considered.

The PP group and the control group received easy-to-prepare boxed meals twice a week (12 meals/week) from Simple Feast (Copenhagen, Denmark); all meals were plant-based (46,47). Both groups received meals that were isocaloric and complied with the national dietary guidelines on macronutrient distribution (283). Moreover, the food items included in the boxes for the PP group were based on a list created as part of the project, which differed between clusters. One meal box included both breakfast and dinner for 3 days, delivered twice a week, meaning that for the days for which meals were not provided (Saturdays) as well as for lunches, participants were referred to the Simple Feast Recipe App. The number of meals provided to the participants was determined using a combination of factors, including budgetary limitations, practical reasons, and behavioral factors. In this app they were shown a set of recommended recipes, so they could prepare meals as similar as possible to the group and cluster to which they were assigned. Meals in the PP group also included some bioactive compounds (i.e., functional ingredients); the compounds were especially (or exclusively)

beneficial for the metabolic function of individuals corresponding to a cluster. Additionally, both groups (PP and control) received a behavioral program delivered through Onmi's app, which is a behavior change technology aimed to increase behavioral flexibility and to facilitate adoption of healthier habits (284). During this program, participants received 2-3 electronic push notifications per week. In the PP group, participants received active "do's" (behavioral prompts) from the predefined Onmi's evidence-based behavioral change program. The do's were based on participants' individual behavior, assessed by questionnaire, and inputs from Eurecat's Nutrition team via the PREVENTOMICS platform. For example, suppose a participant received a recommendation to include kale and Brussels sprouts in their diet. In that case, they might receive a message such as: 'Our analysis shows kale and Brussels sprouts are good for you and should be part of your diet. Find out how much you should be consuming. Do it now' (46). The control group received general messages, which were not given to prompt participants to take a specific action, but mostly informational in nature (i.e., messages based on general guidelines from the National Health Service and the World Health Organization) (46). See Appendix 4.1 for more details about the different behavioral messages for the PP and the control group. More details about the trial protocol can be found elsewhere (46).

Short-term costs and effects

Effects

Different health outcomes were derived from measurements at baseline and follow-up, of which BMI was one (47). Information about quality of life was also measured by the EuroQol five-dimension questionnaire with five levels (EQ-5D-5L) (285). The questionnaire was completed online in Danish. The EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five response levels per dimension; an EQ-5D index score (0 can be considered equal to death and 1 full health) was calculated by using a country specific value set (285,286). The EQ-5D-5L also includes a Visual Analogue Scale (EQ VAS), by which respondents report their perceived health status (285).

Statistical analyses were performed using STATA 17 software (287). Participants' baseline characteristics were described using descriptive statistical analyses. Possible differences between the PP and control groups were also assessed. In case of normal distributed data, an independent t-test was used to test for differences between groups while the Mann-Whitney U test was used in case of non-normality data. The chi-squared test was used to test for differences regarding categorical variables. Linear mixed models (LMMs) were used to quantify the differences in BMI effects between the PP and control group (i.e., difference in outcome measures between baseline and follow-up) (288). The participant's identification was included as random intercept, while all other covariates were included as fixed effects [i.e., time of measurement (visit), intervention group (PP versus control), interaction between time and intervention]. Sex and age were included as fixed covariates as well. The two-tailed significance level was set at α=0.05. Restricted maximum likelihood (REML) was used to fit LMMS to accommodate missing values at random within a single response variable among the

participants' data (289). For analyzing EQ-5D-5L data, a simple linear transformation was done to obtain right-skewed data for the utilities (utility decrements) and generalized estimation equations (GEE) were used to analyze the HRQoL parameters (i.e., EQ-VAS and EQ-5D-5L utilities), using link function, exchangeable correlation structure and robust standard error estimator (290–292). Sex, age, baseline HRQoL, time of measurement (visit) and intervention group (PP versus control), as well as the interaction between time and intervention, were included as fixed covariates.

Costs

Costs were considered from a societal perspective, as proposed in the Danish standards for economic evaluations (293,294), but only intervention costs were assumed relevant societal costs over the trial period (295). Intervention costs were gathered via interviews and by provided information from partners involved in the PREVENTOMICS project. Development costs during the project were not considered, but intervention costs were based upon a hypothetical scenario in which the intervention would enter the market. The costs for the two groups included (1) costs for meals [i.e., food, packaging, production, delivery, indirect costs (see Table 4.1)], (2) behavioral messages, (3) access to the Simple Feast app, and (4) costs for the PREVENTOMICS platform (i.e., storage of data, maintenance questionnaires). In addition, the PP group had costs for (1) the functional ingredients that were added to the meals and for (5) collecting personal data (i.e., blood, urine, and saliva testing/analyses). Which functional ingredient, in what amount and for which price was added to the meals, varied per cluster. The amount is shown in the paper by Aldubayan et al. (47), and the prices per kilogram were 3.84 euros (€), €9.85, €3.73, €2.30 for inulin, fructooligosaccharides, sunflower and turmeric powder, respectively. With the number of participants per cluster, the weighted average price for functional ingredients was calculated.

The costs for the PREVENTOMICS platform were determined as a fixed price. Given that the Danish trial was just one of the clinical trials utilizing the platform (with three other trials conducted as part of the PREVENTOMICS project (8)), the total fixed price was divided by the total number of participants in all trials of the project (N=400). This calculation allowed us to calculate the per-participant costs for utilizing the platform (4). Additionally, the costs for collecting personal data (5) and some cost components of the meals (1) (i.e., the production costs of the meals, indirect costs of the meals) were given per participant but may potentially decrease as the total number of participants increases. However, the exact extent of cost reduction with an increasing number of participants remains uncertain. Costs were given per participant and expressed in 2020 euros, as well as in 2020 Danish krone (DKK).

Table 4.1: Average intervention costs per participant (2020 €; 2020 DKK in brackets).

Components	PP	Control	Difference
(1) Meals (breakfast & dinner, eaten 6 days per week)			
Direct costs			
Food costs	2,746 (20,507)	2,746 (20,507)	0
Packaging costs	1,239 (9,253)	1,239 (9,253)	0
Production costs	1,273 (9,507)	318 (2,375)	955 (7,132)
Delivery costs	189 (1,411)	189 (1,411)	0
Indirect costs (25% of direct costs)[a]	1,362 (10,171)	1,123 (8,387)	239 (1,784)
Functional ingredients	5.00 (37.39)	0	5.00 (37.39)
Total meal costs	*6,814 50,887)*	*5,616 (41,940)*	*1,198 (8,947)*
(2) Behavioral messages via app	15 (112)	15 (112)	0
(3) Access SF app recipes	21 (155)	21 (155)	0
(4) PREVENTOMICS platform (storage data + questionnaires maintenance)[b]	0.81 (6.02)	0.81 (6.02)	0
(5) Tests (blood, urine, saliva)			
Omics	383 (2,857)	0	383 (2,857)
Genetics	54 (403)	0	54 (403)
Other (e.g., overhead)	115 (857)	0	115 (857)
Total tests costs	*551 (4,117)*	*0*	*551 (4,117)*
TOTAL COSTS	**7,402 (55,277)**	**5,653 (42,215)**	**1,749 (13,062)**

DKK Danish Krone, *PP* Personalized Plan, *SF* Simple Feast.
[a] Indirect costs (indicated to be 25% by SF) cover, for example: electricity, water consumption, use of own premises (i.e., SF resources that are not salaries for the production of the meal boxes).
[b] A fixed amount of €140 per month was charged. These costs were divided over the total number of users of the platform, which equaled the total number of participants in all interventions in the PREVENTOMICS project (N=400).

Long-term cost-effectiveness

Method to estimate long-term outcomes

Since the trial duration was too short to capture all relevant costs and effects, a Markov model for obesity with obesity-related diseases was used to estimate lifetime costs and health outcomes (281). The model was developed as part of a European Union (EU)-funded project (COMPAR-EU) (213). Figure 4.1 provides an overview of the model's structure (281). Each rectangle shows a different health state. The model starts with a cohort of people with overweight or obesity and a certain distribution in man/women, a mean age, and a mean BMI (based on the population in the Danish trial) in the state titled 'no diabetes/no ischemic heart disease (IHD)/no stroke.' The model then simulates what can happen over time in this cohort regarding the occurrence of diabetes, IHD, stroke and death; these diseases were included in the model, since their prevalence and costs are the highest amongst obesity-related diseases (214,215). A cycle length of 1 year was used to model over a lifetime horizon.

Disease incidence and mortality are dependent on sex, age, BMI, and health state. Incidence of IHD is for example higher for patients in the diabetes state than patients in the

'no diabetes/no IHD/no stroke' state (281). Mortality in the diabetes state encompasses both diabetes-related mortality and mortality due to other causes. IHD, including myocardial infarction (MI), and stroke are events associated with a significant risk of mortality when they occur. As a result, mortality for these disease states has been subdivided into case fatality, IHD- or stroke-related mortality, and mortality due to other causes (281).

BMI is included as a continuous variable in this model. All analyses were performed in R using RStudio (version Ri386 3.6.1/ Rx64 3.6.1). Details of the model can be found elsewhere (281).

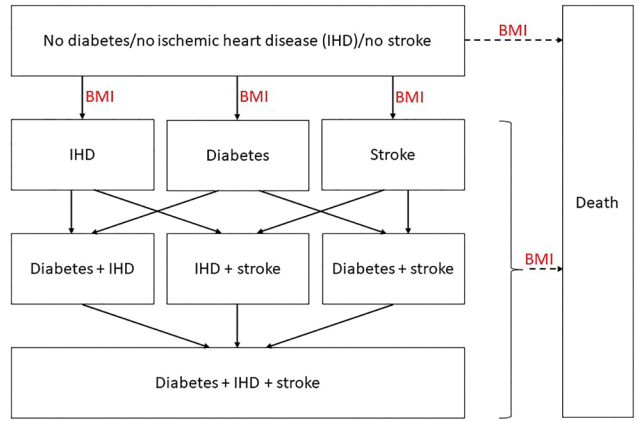


Figure 4.1: Structure of the Markov model for obesity as described by Hoogendoorn et al. (281). *BMI* body mass index, *IHD* Ischemic heart disease.

Model inputs

For the analysis, we used data from the Danish intervention study in the PREVENTOMICS project. Other sources were used to derive the demographic and epidemiological distributions of the Danish population for estimating the transition probabilities, as well as to describe the associated HRQoL and costs in each health state. Model inputs are described in the following sections and presented in Table 4.2; details are described elsewhere (281).

Demographic and epidemiological input for transition probabilities

The model included mean BMI by sex and age of the Danish population, and this was obtained from the Global Burden of Disease study (216). The sex-specific relative risks for the association between BMI and all-cause mortality were obtained from a meta-analysis of 230 cohort studies (208). The Global Burden of Disease study was used for the relative risks by age for the association between BMI and diabetes, IHD and stroke (216). Additionally, the relative risks for the co-occurrence of diabetes and stroke and diabetes and IHD were considered; risks for co-occurrence of IHD and stroke were assumed equal to the risks for diabetes and

IHD (217–219). Data on the prevalence and incidence for diabetes, IHD and stroke, specified by sex and age were obtained from the DYNAMO-HIA study; mortality data were also obtained from this study (217,218). Moreover, three additional studies (220–222) and OECD data were used to calculate mortality (223,224). No fixed transition probabilities are given in Table 4.2 since they varied according to age, sex, and BMI (281).

Effectiveness

The mean change in BMI was used as one of the intervention effects and was obtained from the Danish trial (47). Since this change was observed over the 10-week trial period, an assumption had to be made about changes in BMI beyond the trial's follow-up period. On the basis of the study conducted by Knowler et al. (296), we assumed that the treatment effect in terms of BMI reduction would gradually decline in subsequent years. Specifically, the annual percentage of treatment effect loss in BMI was estimated to be 17.9% until the beginning of year 5, after which any remaining BMI reduction was assumed stable (see more explanation below Table 4.2) (296). This assumption was deemed reasonable for two reasons: firstly, the behavioral prompts provided as part of the intervention were expected to lead to sustained treatment effects beyond the intervention period, as supported by previous research indicating the role of behavioral flexibility in maintaining long-term health behaviors (297,298). Secondly, participants in the intervention group were exposed to new, healthier, and more suitable ideas for cooking meals during the intervention, which they could continue to apply, and could therefore lead to a sustained intervention effect.

The other intervention effect used in the cost-effectiveness model was the change in utility (mean) obtained from the trial (see section 'effects'). The long-term health outcomes, as recommended in the guideline (293,294), were expressed in life expectancy and quality-adjusted life years (QALYs), which were estimated using the model (281). HRQoL in the model was based on general population sex- and age-specific utilities, based on EQ-5D values in Denmark (299). These utilities were adjusted for the occurrence of diabetes, IHD and stroke using prevalence data and previously published utility decrements for the different diseases (226). All utilities were discounted at 4% per year (293,294,300).

Costs

Total costs of the intervention (see section 'costs') were applied only during the first cycle (i.e., costs were applied during the intervention period and assumed to be zero afterwards). Direct medical costs for treating diabetes, IHD and stroke were obtained from different studies (300–303).

Costs of productivity loss were estimated using SHARE data (245) on the basis of values for central European countries since the employment status in Denmark is comparable with those in central European countries (304,305). The costs for long-term work loss were calculated using SHARE data (245) on the percentage of people with a paid job, the mean number of working hours per week and the probability of unemployment using the friction

cost method (friction period of 3 months (306)). Production costs per hour were also obtained from the Eurostat website (307). See Appendix 4.2 for more details. Costs for informal care were based on SHARE data (245) and calculated using information on the percentage of people receiving informal care and the number of hours per day on the basis of regression equations for northern European countries.

Unrelated medical costs (i.e., costs for other diseases than obesity-related diseases) were calculated by subtracting the related costs per capita for diabetes, IHD and stroke from the annual healthcare spending by capita by sex and age. More information about this calculation is shown in Appendix 4.3. Non-medical costs were age specific and estimated from national household consumption/expenditure surveys in each country [Household Budget Surveys (HBS) from Eurostat]. The non-medical costs were based on mean consumption expenditure (308) by taking into account household size (309) and by correcting for the probability of having more than one adult per household (244). See Appendix 4.4 for more details.

All costs were converted to 2020 currency using the consumer price index for Denmark (310). Thereafter, as recommended by the ISPOR's guideline on good research practices (311), the costs were converted to DKK using purchasing power parity (PPP) (312) and exchange rates (313), depending on the source. All costs were then converted from 2020 DKK to 2020 € using exchange rates (1 DKK= €0.134) (313). Costs were discounted at 4% annually (293,294,300).

Base-Case Analysis

Model outcomes consisted of total costs (including a breakdown by cost component), life years, life years with diabetes, cumulative incident cases of IHD and stroke, and QALYs of the PP and control interventions. The incremental cost-utility ratio (ICUR) was calculated by dividing the incremental costs by the incremental QALYs (PP versus control). The gross domestic product (GDP) per capita in Denmark in 2020 (€47,817, or 357,100 DKK) was used as the willingness to pay threshold (WTP) to gain one QALY, as done in earlier studies (300,314), since no specific threshold value was recommended in the guideline (293,294).

Table 4.2: Model inputs.

Parameter	Deterministic value	Sensitivity analysis range (CI (95%) or assumption)	Distribution	Source
General				
Time horizon, years	Lifetime	-	-	-
Cycle length	1 year	-	-	-
RRs for association BMI and diabetes, IHD and stroke	RR varied by BMI, specified by age.	-	Normal distribution	GBD (216)
RRs for the co-occurrence of diseases	RR specified by age and sex.	-	Fixed	Different sources (217–219)
RRs for association BMI and all-cause mortality	RR varied by BMI, specified by sex.	-	Normal distribution	Aune et al.(208)
Disease prevalence, incidence, and mortality	Based on sex and age specific prevalence, incidence, and mortality data, specified by BMI and divided over the different health states in the model with RRs[a]	-	Fixed	Different sources (208,216–224)
Discount rate:				
Costs	4%	-	-	Ehlers et al.(300)
Effects	4%	-	-	Alban et al.(293)
Population:				
Proportion males, %	31%	-	-	Percentage in trial
BMI, at start	32.14	-	-	Mean in trial
Age, at start	46.12	-	-	Mean in trial
Effects				
Intervention effect PP (versus control):				
Effect BMI, kg/m^2 (SE)	-0.07 (0.23)	-0.51, 0.38	Normal distribution	Trial results, Aldubayan et al.(47)
Effect loss BMI per year, percentage (proportion)	17.9% (0.1786)[b]	+/- 20%	-	Knowler et al.(296)

Table 4.2: Continued.

Parameter	Deterministic value	Sensitivity analysis range (CI (95%) or assumption)	Distribution	Source
Duration effect loss BMI, year	5	1-7	-	Assumption based on Knowler et al.(296)
Intervention effect PP (versus control): Effect HRQol, EQ-5D-5L utilities (SE)	0.04 (0.02)	0.00, 0.07	Normal distribution	Trial results
Duration effect HRQol (intervention period), years	0.19	0.19-10	-	Trial duration, Aldubayan et al.(47)
QALY – utility decrements for obesity-related diseases:				
Diabetes	-0.069	-	Fixed	Sullivan et al. & Sørensen et al.(226,299)
IHD	-0.061	-	Fixed	
Stroke	-0.114	-	Fixed	
Costs 2020 € (DKK)				
Total intervention costs:				
PP:	7,402 (55,277)	+/- 20%	Normal distribution	Trial data
Control:	5,653 (42,215)	+/- 20%		Trial data
Duration effect costs (intervention period), years	0.19	-	-	Trial duration, Aldubayan et al.(47)
Treatment of diseases:				
Diabetes[c]	6,342 (47,363)	+/- 20%	Gamma	Sortsø et al.(303)
IHD first year	19,677 (146,950)	+/- 20%	Gamma	Ehlers et al.(300) & Brorholt et al.(302)
IHD subsequent year	480 (3,585)	+/- 20%	Gamma	Ehlers et al.(300) & Brorholt et al.(302)
Stroke first year	16,300 (121,729)	+/- 20%	Gamma	Ehlers et al.(300) & Jennum et al.(301)
Stroke subsequent year	2,896 (21,628)	+/- 20%	Gamma	Ehlers et al.(300) & Jennum et al.(301)
Productivity loss:				
Hourly rate:	45.3 (338)	+/- 20%	Gamma	Eurostat (307)

Table 4.2: Continued.

Parameter	Deterministic value	Sensitivity analysis range (CI (95%) or assumption)	Distribution	Source
Informal care: Hourly rate:	21.0 (157)	+/- 20%	Gamma	Ecorys (315)
Unrelated medical costs	Depending on age and sex (+ divided by 'last year of life' and 'other years of life')	+/- 20%	Gamma	Different sources (see Appendix 4.3)
Non-medical costs	Depending on age and sex	+/- 20%	Gamma	Different sources (239,308,309)

BMI Body Mass Index, *CI* confidence interval, *DKK* Danish Krone, *EQ-5D* EuroQol five-dimension questionnaire, *HRQoL* Health-related quality of life, *IHD* ischemic heart disease, *kg* kilogram, *m* meter, *PP* Personalized Plan, *QALY* quality-adjusted life years, *RR* relative risk, *SE* standard error.
[a] See Hoogendoorn et al.(281) for methods regarding the calculation of transition probabilities.
[b] Knowler et al.(296) observed over a 5-year period that participants in the study experienced an annual percentage of decreasing effect in weight loss, starting with 100% weight loss (approximately 7 kilograms) in the first year, followed by a gradual gain in weight, resulting in 28.5% of weight loss (approximately 2 kilograms) from the initial 7 kilograms at the beginning of year 5. This translates into an average annual decrease of 17.86% in weight loss.
[c] These are the costs for type 2 and type 1 diabetes together. No literature was found that separated these costs for type 2 diabetes only. However, literature showed that prevalence was higher for type 2 diabetes compared to type 1 (316).

Sensitivity analyses

Univariate sensitivity analyses and scenario analysis

Several sensitivity analyses were conducted to examine the robustness of the results. Univariate sensitivity analyses were performed to estimate the impact of individual key model parameters or assumptions on the outcomes. Input parameters were varied individually according to the lower and upper limits of the 95% CI, while all other parameter values were kept constant. If the CI was unavailable, which was the case for the proportion of effect loss per year and different cost components, a variation of 20% was used. The uncertainty in intervention costs (+/-20%) reflects, among other things, the uncertainty in the assumption in the number of people receiving the intervention. The results were presented in three tornado diagrams: one for incremental effectiveness (QALYs), one for incremental costs and one for the ICUR. Moreover, a scenario analysis was performed in which non-medical and unrelated costs were excluded, since some have argued for their exclusion in cost-effectiveness analyses (317). We did not include subgroup analyses since heterogeneity was not studied in the trial analyses, mainly because of sample size limitations (47,318).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed with enough iterations (5,000) to obtain stable estimates of relevant parameters. Uncertainty around the relative risks for the association of BMI with all-cause mortality and the relative risks for BMI and obesity-related diseases were incorporated in the PSA. Moreover, uncertainty around costs was included and all other parameters were kept fixed (e.g., utility decrements) (see Table 4.2). See Appendix 4.5 for more information on the PSA inputs. Results were presented in a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) (319).

RESULTS

Short-term costs and effects

In the actual trial, a total of 100 Danish participants started the intervention period at baseline. The results of the baseline characteristics can be found in Table 4.3. As expected, given the randomized allocation of participants, no significant differences in age, gender, BMI and EQ-5D-5L utility were observed. However, there were significant differences in baseline EQ-5D VAS. Details about other parameters can be found elsewhere (47).

Table 4.3: Baseline characteristics.

	PP, N=49			Control, N=51			*p*-Value[a]
	Mean (sd)	*Median (IQR)*	*N (%)*	*Mean (sd)*	*Median (IQR)*	*N (%)*	
Age, years	46.39 (11.85)	46.92 (35.35, 55.73)	-	45.86 (11.36)	47.27 (38.81, 54.73)	-	0.91
Sex							
Females	-	-	37 (76)	-	-	32 (63)	0.17
Males	-	-	12 (24)	-	-	19 (37)	
BMI (kg/m²)	31.98 (3.61)	31.68 (29.12, 33.74)	-	32.29 (3.62)	31.41 (29.38, 34.30)	-	0.73
EQ-5D-5L utility	0.92 (0.12)	0.95 (0.88, 1)		0.94 (0.08)	0.95 (0.88, 1)		0.68
EQ-5D VAS	74.33 (15.58)	80 (65, 85)		81.61 (13.56)	85 (75, 90)		0.01

BMI body mass index, *EQ-5D* EuroQol five-dimension questionnaire, *IQR* interquartile range, *kg* kilogram, *m* meter, *n* number, *PP* Personalized Plan, *sd* standard deviation, *VAS* Visual Analogue Scale.
[a]If the values for both the PP and the control groups were normally distributed, the *p*-values of the means were given; if not, the *p*-values of the medians were given.

In total, 82 respondents finished the study (38 in the PP group and 44 in the control group. In both groups a significant decrease in BMI was observed compared with baseline measures (Table 4.4). Moreover, the PP group showed a slightly greater but nonsignificant decrease in BMI compared with the control group. A significant difference in EQ-5D-5L utility of 0.04 was found. Additionally, the PP group reported greater increases in EQ-5D VAS than the control group; however, these results were not statistically significant.

Table 4.4: Results of the 10-week clinical trial.

Variables	Effect in PP, means (SE)	Effect in control, means (SE)	Mean difference PP-control (95% CI)	*P*-Value
BMI (kg/m²)	-1.05 (0.17)**	-0.98 (0.15)**	-0.07 (-0.51, 0.38)	0.76
EQ-5D utilities	0.02 (0.01)	-0.02 (0.01)	0.04 (0.00, 0.07)	0.04
EQ-5D VAS	4.74 (1.82)**	2.05 (1.23)	2.69 (-1.61, 7.00)	0.22

BMI body mass index, *CI* confidence interval, *EQ-5D* EuroQol five-dimension questionnaire, *kg* kilogram, *m* meter, *PP* Personalized Plan, *SE* standard error, *VAS* Visual Analogue Scale.
**p* < 0.05 significantly change from baseline
***p* < 0.01 significantly change from baseline

When costs of the two interventions were analyzed, a difference in total costs of €1,749 was found (Table 4.1). This mainly arose from the costs of preparing and providing the meals. Personalized meals were more labor intensive and therefore more costly, since more unique boxes needed to be prepared. Moreover, functional ingredients were incorporated into the

personalized meals. Table 4.1 presents weighted average costs for these ingredients. The costs for the tests represented a one-time expenditure.

Base-case estimates of lifetime costs and effects

Table 4.5 provides the base-case results for various outcomes over a lifetime. Regarding discounted health outcomes, PP increased health by 0.011 QALYs (PP:15.117 versus control: 15.106). Regarding discounted costs, PP increased total lifetime societal costs by €1,736 (12,963 DKK) (PP: €520,102 versus control: €518,366). The most important factor in this increase was intervention costs. Increases were found in unrelated costs and non-medical costs. On the contrary, there was a decrease in the costs of different obesity-related diseases and productivity costs. When the differences in QALYs and costs were combined, the additional cost for PP to gain one QALY was €158,798 (1,185,909 DKK). This is much higher than the WTP threshold of €47,817 per QALY gained (357,100 DKK), meaning that PP is not cost-effective given that threshold. The undiscounted results show higher effects and higher costs than the discounted results, resulting in a lower ICUR [€99,575 (743,632 DKK)] compared with the discounted ICUR.

Table 4.5: Base-case scenario results (deterministic).

	Discounted at 4%			Undiscounted		
	PP	Control	Difference	PP	Control	Difference
Effects						
Life years	17.766	17.763	0.003	34.092	34.081	0.011
Life years with diabetes	2.769	2.781	-0.012	7.016	7.040	-0.024
Cum. Incident cases[a] diabetes/1000	377.255	378.201	-0.946	377.255	378.201	-0.946
Cum. Incident cases[a] IHD/1000	279.448	279.788	-0.34	279.448	279.788	-0.34
Cum. Incident cases[a] stroke / 1000	315.719	316.094	-0.375	315.719	316.094	-0.375
QALYs	15.117	15.106	0.011	28.483	28.464	0.019
Costs (in 2020 € (DKK))						
Diabetes	18,118 (135,305)	18,193 (135,864)	-75 (-559)	46,769 (349,272)	46,926 (350,445)	-157 (-1,173)
IHD	2,910 (21,732)	2,916 (21,774)	-6 (-43)	7,219 (53,915)	7,230 (53,997)	-11 (-82)
Stroke	3,642 (27,199)	3,649 (27,252)	-7 (-53)	10,775 (80,465)	10,791 (80,586)	-16 (-121)
Unrelated	137,618 (1,027,739)	137,602 (1,027,616)	17 (124)	336,862 (2,515,695)	336,763 (2,514,958)	99 (737)
Non-medical	327,597 (2,446,504)	327,536 (2,446,050)	61 (454)	652,691 (4,874,319)	652,465 (4,872,636)	225 (1,684)
Intervention[a]	7,402 (55,277)	5,653 (42,215)	1,749 (13, 062)	7,402 (55,277)	5,653 (42,215)	1,749 (13,062)
Informal care	5,581 (41,680)	5,582 (41,683)	0 (-3)	16,169 (120,753)	16,164 (120,713)	5 (41)
Productivity	17,234 (128,703)	17,236 (128,772)	-3 (-19)	24,668 (184,221)	24,670 (184,240)	-2 (-18)
TOTAL	520,102 (3,884,138)	518,366 (3,871,175)	1,736 (12, 963)	1,102 ,555 (8,233,918)	1,100,663 (8,219,788)	1,892 (14,129)
ICUR	***158,798 (1,185,909)***			***99,575 (743,632)***		

Cum. Cumulative, *DKK* Danish Krone, *ICUR* incremental cost-utility ratio, *IHD* Ischemic heart disease, *PP* Personalized Plan, *QALYs*, quality-adjusted life years.
[a]Not discounted

Univariate sensitivity analyses and scenario analysis

Results from the univariate sensitivity analyses of different parameters are shown in Figure 4.2A-C. The change in intervention costs had the most impact on the incremental costs, followed by the intervention's effect on BMI (see Figure 4.2A). The most impactful parameter for the incremental QALYs was the duration of the QoL effect (see Figure 4.2B); an increase in duration of 0.19 years (trial period) to 10 years increased the incremental QALYs from 0.011 to 0.324. The second most influential parameter was the intervention's effect on BMI.

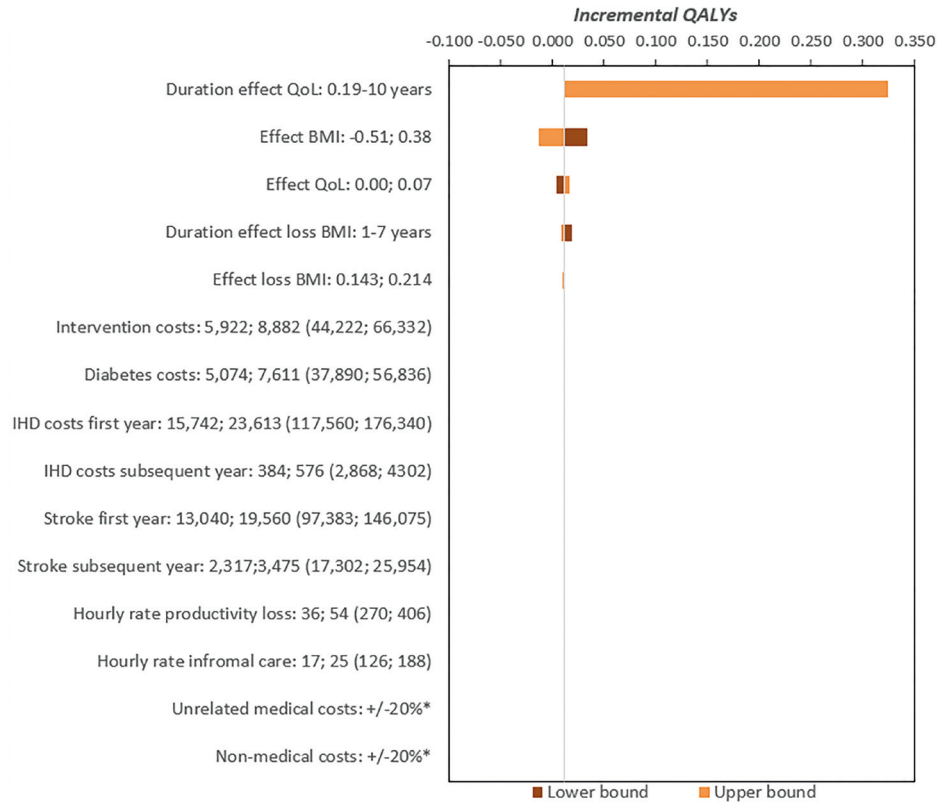
When the impact of varying individual parameters on the ICUR was explored (Figure 4.2C), it was found that the effect in HRQoL (short-term trial effect) had the most impact. When the upper limit of the 95% CI for the treatment's effect on utility was used (i.e., 0.07 as presented in Table 4.4), the ICUR decreased from €158,798 per QALY (1,185,909 DKK) to €105,823 per QALY (790,293 DKK). When the lower limit of the 95% CI of the other effect measure (i.e., BMI) that was obtained from the trial was used (i.e., -0.51 kg/m^2 as presented in Table 4.4) an ICUR of €49,626 per QALY gained (370,610 DKK) was found. This change in parameter did not result in an ICUR below the WTP threshold of €47,817 (357,100 DKK). When the upper limit was used (i.e., 0.38 kg/m^2), the PP intervention was dominated by the control. A 20% reduction in intervention costs resulted in an ICUR of €23,668 per QALY gained (174,534 DKK), which is cost-effective given a WTP of €47,817 (357,100 DKK). Given the close relationship between intervention costs and the ICUR, we varied the reductions in intervention costs to explore their impact on the ICUR (see Figure 4.3). We found that if intervention costs were reduced by 16%, the ICUR was equal to the WTP threshold of €47,817 (357,100 DKK). This translates into a reduction of €1,213 (9,060 DKK) per person. Cost savings were even observed when intervention costs were reduced by more than 23%.

One scenario analysis was carried out, in which the non-medical costs and unrelated medical costs were excluded from the calculations. This resulted in a slight decrease in the incremental costs [€1,658 (12,385 DKK)], leading to an ICUR that was lower than the base-case estimate, though still not cost-effective [€156,173 per QALY (1,166,309 DKK)]. See Appendix 4.6 for detailed results of this scenario analysis.

A


Incremental costs € (DKK)
0 (0)
670 (5,000)
1,339 (10,000)
2,009 (15,000)
2,678 (20,000)
3,348 (25,000)
Intervention costs: 5,922; 8,882 (44,222; 66,332)
Effect BMI: -0.51; 0.38
Duration effect loss BMI: 1-7 years
Diabetes costs: 5,074; 7,611 (37,890; 56,836)
Non-medical costs: +/-20%*
Effect loss BMI: 0.143; 0.214
Unrelated medical costs: +/-20%*
IHD costs first year: 15,742; 23,613 (117,560; 176,340)
Stroke subsequent year: 2,317;3,475 (17,302; 25,954)
Stroke first year: 13,040; 19,560 (97,383; 146,075)
Hourly rate productivity loss: 36; 54 (270; 406)
IHD costs subsequent year: 384; 576 (2,868; 4302)
Hourly rate infromal care: 17; 25 (126; 188)
Effect QoL: 0.00; 0.07
Duration effect QoL: 0.19-10 years
Lower bound
Upper bound

B


Incremental QALYs
-0.100 -0.050 0.000 0.050 0.100 0.150 0.200 0.250 0.300 0.350
Duration effect QoL: 0.19-10 years
Effect BMI: -0.51; 0.38
Effect QoL: 0.00; 0.07
Duration effect loss BMI: 1-7 years
Effect loss BMI: 0.143; 0.214
Intervention costs: 5,922; 8,882 (44,222; 66,332)
Diabetes costs: 5,074; 7,611 (37,890; 56,836)
IHD costs first year: 15,742; 23,613 (117,560; 176,340)
IHD costs subsequent year: 384; 576 (2,868; 4302)
Stroke first year: 13,040; 19,560 (97,383; 146,075)
Stroke subsequent year: 2,317;3,475 (17,302; 25,954)
Hourly rate productivity loss: 36; 54 (270; 406)
Hourly rate infromal care: 17; 25 (126; 188)
Unrelated medical costs: +/-20%*
Non-medical costs: +/-20%*
Lower bound
Upper bound

C

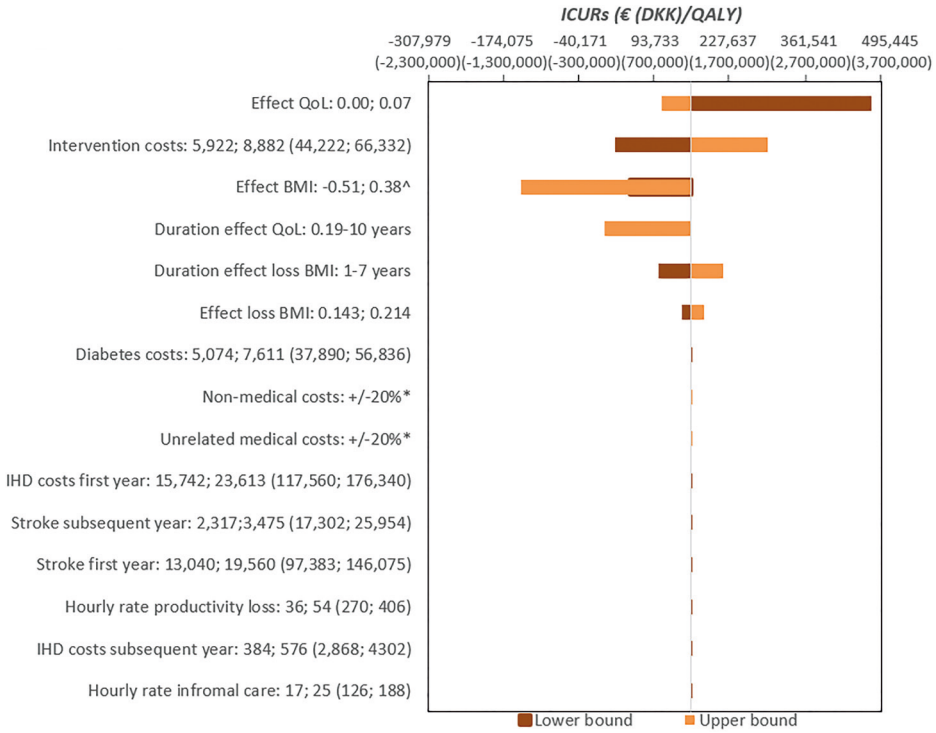


Figure 4.2: Tornado diagrams for change in incremental costs in € (DKK) (A), incremental QALYs (B) and ICUR (C) using lower and upper bounds of parameters. *BMI* Body Mass Index, *DKK* Danish Krone, *ICUR* incremental cost-utility ratio, *IHD* ischemic heart disease, *QALYs* quality-adjusted life years, *QoL* quality of life. *No fixed number, since costs differ by sex and age. ^Parameters for both lower and upper bounds lead to results in the same direction (the control intervention dominates when the upper bound was used as input).

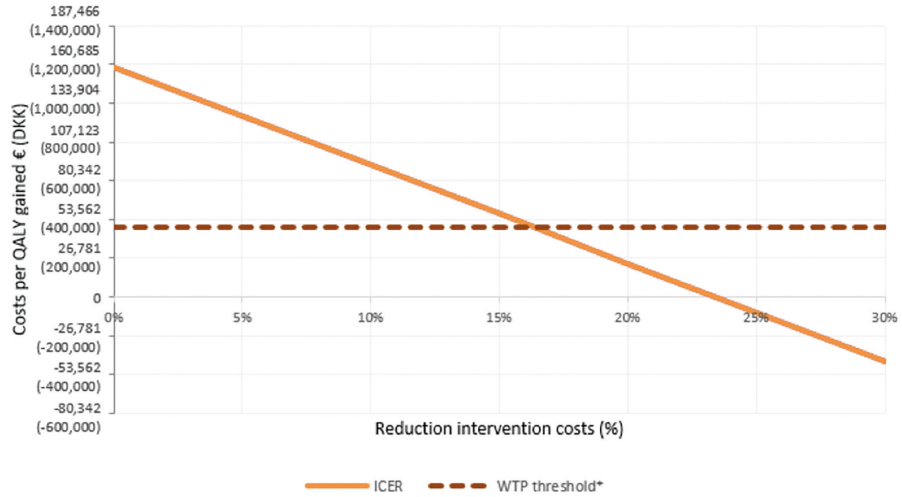


Figure 4.3: Influence of reduction in intervention costs on cost-effectiveness. *QALYs* quality-adjusted life years *DKK,* Danish Krone, *ICUR* incremental cost-utility ratio, *WTP* willingness to pay. *WTP threshold = 357,100 DKK per QALY gained (€47,817).

Probabilistic Sensitivity Analysis (PSA)

Figure 4.4 shows an incremental cost-effectiveness scatterplot with discounted costs and QALYs. Most values can be found in the northeast quadrant (80%), meaning that PP is more costly and more effective than the control intervention. Moreover, the results show that most ICURS are above the maximum WTP threshold, meaning that the probability of PP to be cost-effective is low; only 3% of the iterations were found to be cost-effective at a threshold of €47,817 (357,100 DKK). This finding is supported by Figure 4.5, in which the cost-effectiveness acceptability curve is shown. Figure 4.5 shows that by a WTP threshold of €200,856 (1,500,000 DKK) the probability of PP being cost-effective is 57%. Based on the PSA results, the mean QALY gain from PP is 0.011 (95% CI: -0.015, 0.04) and mean cost increase is €1,748 (13,055 DKK) [95% CI: €1,592 (11,892 DKK), €1,907 (14,239 DKK)].

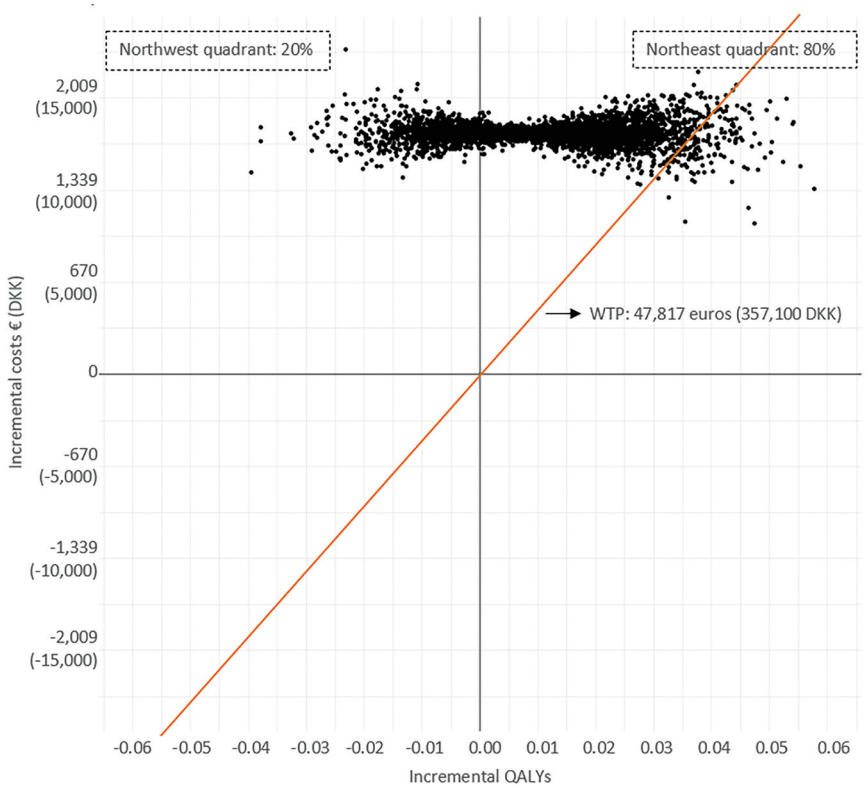


Figure 4.4: Probabilistic sensitivity analysis of the cost-effectiveness of PP versus control. *QALYs* quality-adjusted life years *DKK,* Danish Krone, *PP* personalized plan, *WTP* Willingness to Pay.

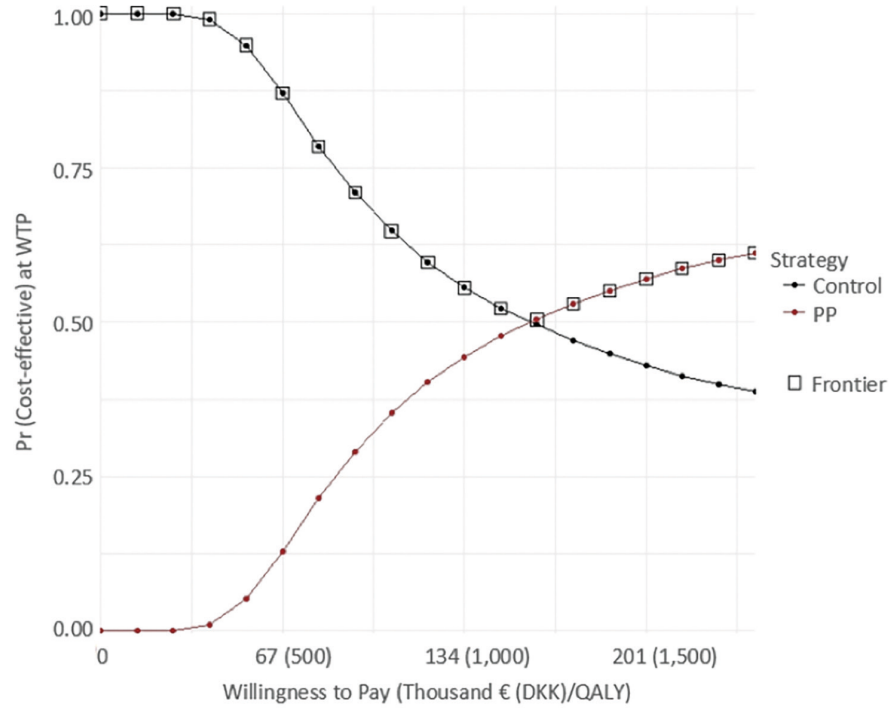


Figure 4.5: Cost-effectiveness acceptability curve plot. *DKK* Danish Krone, *PP* Personalized Plan, *Pr* probability, *QALY* quality-adjusted life year, *WTP* Willingness to Pay.

DISCUSSION AND CONCLUSION

This economic evaluation was based on a randomized controlled trial comparing a personalized intervention using omics science (PP) with a control intervention (non-personalized). In both groups, participants received home-delivered meals and behavioral messages, but the PP group received meals and messages that were based on individual phenotypic characteristics at the metabolome level, genotype, lifestyle habits and preferences. In our study, we examined both the short-term and long-term costs and health outcomes associated with PP compared with the control intervention. The trial showed statistically nonsignificant differences in clinical outcomes (i.e., BMI change of -0.07 kg/m^2 (95% CI: -0.51, 0.38) between the PP and control groups. When the short-term differences in effectiveness were extrapolated into lifetime effectiveness in QALYs, we found a slight increase of 0.011 QALYs when the PP intervention was compared with control. The costs increased as well [€1,736 (12,963 DKK)], resulting in base-case results that were not cost-effective (€158,798) at a given WTP threshold of €47,817 per QALY gained (357,100 DKK).

However, the limited statistical power, reflected in wide 95% CIs surrounding the estimated short-term effects, makes it important to address the uncertainty in cost-effectiveness results

with sensitivity analyses. Results from the PSA showed that there was only a small probability (3%) that PP was cost-effective. From the univariate analyses we found again that the results were quite robust; for most parameters, varying their values did not substantially affect the cost-effectiveness estimates. However, as expected, a 20% reduction in intervention costs reduced the ICUR to €23,668 per QALY gained (174,534 DKK), which is cost-effective given a WTP of €47,817 (357,100 DKK). This was even the case if intervention costs were reduced by 16%. Overall, there are only small increases in QALYs observed when PP was compared with control and the incremental costs were relatively high. This can mainly be explained because personalization of nutrition is labor intensive, which makes intervention costs high; data need to be collected, organized, and analyzed (173). For some intervention costs (i.e., the production costs of the meals, indirect costs of the meals, costs for testing and costs for the DSS), the costs per participant, and thereby the total intervention costs, could be reduced by increasing the volume (i.e., number of users). In other words, PP might be cost-effective when compared with the control group if the intervention were to be scaled up. This is something which should be validated in future research.

The results from our study correspond with a recently conducted systematic literature review that investigated the cost-effectiveness of interventions with a personalized nutrition component in adults (280). That review included 49 studies and found that personalized nutrition interventions often led to incremental QALYs between 0 and 0.1, which is comparable with our study findings. However, the review concluded that most personalized nutrition interventions were cost-effective, which is somewhat different from our CEA results. This could mainly be explained by the lower incremental costs found in the review [most costs between -2,000 (-€1,886) and +2,000 dollars (+€1,886)] compared with the incremental costs in our study (+€1,736). The lack of studies exploring personalized nutrition interventions based on omics-science, which incurs higher costs (48), could account for this finding. Instead, the reviewed studies personalized interventions using psychological data, while some incorporated basic biological data such as plasma fatty acids (150,158) and vitamin or protein intake (128,166). However, none of them employed advanced omics technologies as seen in the PREVENTOMICS project.

Different choices need to be made when analyzing the cost-effectiveness of nutrition interventions (e.g., how to deal with 'weight loss'), and this results in heterogeneity in methods across CEAs (280,320–323). In our study, we used the clinical trial results regarding BMI as a proxy for 'weight loss' as model input. However, some authors believe that it might be better to use other outcome measures than BMI (324). For example, body fat might be a better measure for 'weight loss' since it is the most metabolically harmful tissue type (194,325). We, however, decided to stick to BMI as our outcome measure for several reasons. First, a validated economic model has been used to explore the cost effectiveness of PP (281). This model used BMI as a continuous parameter, unlike most previously published obesity models that include classes (e.g., normal weight, overweight and obese) (260). Modeling BMI as a continuous parameter gives the model more flexibility in simulating the impact of personalized nutrition on BMI.

There were not enough data available in the literature to do this with similar other outcome measures, such as body fat. Second, if we had used another outcome, we would have had to work with intermediate outcome measures; for example, body fat had to be transformed into BMI before calculating lifetime cost-effectiveness. This is not recommended in good research practice guidelines for cost-effectiveness analysis alongside clinical trials (326). Third, studies have shown that there is a strong correlation between body fat and BMI (327), which was also found in the Danish trial results (47); small (insignificant) decreases were found when PP was compared with control), so we would not expect different results if a different 'weight loss' measure was used as input for the model.

Additionally, the choice for a specific comparator also varied in economic evaluations of (personalized) nutrition interventions, and this might influence the cost-effectiveness results of personalized nutrition (280). In our study, we used a control intervention that is already considered a 'healthy' option. It might therefore be the case that the benefits of additional personalization might not be worth the extra money, particularly given the high intervention costs that were observed for personalization. The question is then, will payers accept the necessary higher short-term costs (e.g., intervention costs) to achieve any long-term health benefits?

Another important question to consider is who the payers for personalized nutrition interventions will be. Nutrition interventions are typically paid out-of-pocket by the consumer and are thus not reimbursed by a third-party payer (321). Higher social economic groups might therefore be more likely to use personalized nutrition, although literature showed that in high-income countries the obesity epidemic affects people with a lower socioeconomic status disproportionately (328). Personalized nutrition might thereby ignore the underlying population causes of obesity (i.e., social, cultural, economic, and political contexts) and might increase social inequalities further. Some governments may therefore find it important to make personalized nutrition acceptable for everyone and could consider introducing reimbursement or subsidies for effective personalized nutrition interventions.

This study has several limitations that should be considered. First, the costs were presented in 2020 euros instead of a more current year closer to the time of publication. However, considering the inflation that has occurred since 2020, it is anticipated that the difference in costs between PP and control would only increase (310). This, in turn, does not alter the ultimate conclusion that PP is not cost-effective since greater incremental costs would only increase the ICUR values. Second, although short-term effectiveness data were based on an appropriately designed and executed clinical trial, the trial population was relatively small, which resulted in limited statistical power and a rather wide 95% CI for BMI reduction. As a result, subgroup analyses were therefore not conducted. It would be desirable to perform a similar study with a larger population. Third, the trial's follow-up might have been too short to capture the full effect of personalized nutrition. Given that personalized nutrition is an individual-tailored approach, it is likely that compliance with such interventions is higher,

which could lead to sustained positive behavioral changes and greater long-term effectiveness regarding outcomes such as BMI (36). However, this is likely not directly captured in our study due to the short follow-up. Our study findings, which mainly show insignificant short-term results, are in line with a previous study indicating that the most significant improvements by nutrition interventions occur after the first 6 months (329). This highlights the need for properly funded long-term studies to effectively address the serious health consequences of obesity.

As with most clinical trial-based evaluations, the short study follow-up necessitated modeling assumptions to estimate lifetime cost-effectiveness. For example, assumptions were made over the annual percentage of effect loss in BMI after the first year, based on the literature (296), which is not as precise as if we had been able to measure this for a longer time. However, we found consistency in literature about this effect loss (330). Moreover, we examined the impact of the uncertainty around the assumptions that we made in our sensitivity analyses. This study is therefore meant as a starting point for future studies of the cost-effectiveness of personalized nutrition interventions.

Although cost-effectiveness is an important factor in policymaking decisions about interventions, other factors are relevant as well. One approach to examine all relevant factors would be a comprehensive health technology assessment (HTA) (71,331,332), where interventions are systematically evaluated and assessed in the context of clinical, ethical, economic, social, legislative, organizational, and other domains. This HTA should include results from preference studies as well, since knowledge about people's preferences regarding personalized nutrition interventions could lead to the development of more cost-effective interventions that people need and accept (60). Moreover, this research could be extended to other countries as well, to see if similar cost-effectiveness results are found (281).

We found that PP would not be considered cost-effective based on the point estimate for BMI reduction seen in the clinical trial but found that PP has the potential to yield health benefits when compared with a control. A larger and/or longer study would provide a more accurate estimate of effectiveness. Moreover, scaling up the intervention would reduce per-patient costs and thereby help to make the intervention cost-effective. In addition to the challenges in demonstrating the cost-effectiveness of personalized nutrition interventions, another challenge relates to how they will be financed; options to consider are needs-dependent reimbursements or subsidies.

APPENDICES

Appendix 4.1: The type and number of behavioral messages delivered by ONMI to the participants in the personalized and control groups, as presented by Aldubayan et al. 2022 (46).

Type of messages	Quantity	Description	Example	PP	C
Starter Do	1	Easy start of the programme on behavioural questionnaire completion at V2	SWITCH SEATS DAY! Move some seating around today. Sit somewhere different at meals/ when working/when watching TV. Get a new view!—Shaking up old habits is good for you and puts you back in charge of your life. Try something new regularly. Make every day count! --	✓	✓
General Do	5	Apply to everyone, relatively easy, to get user hooked to the programme	NEW WAY DAY. Take a detour today, go the prettiest route not the shortest. Allow more time, smile at people. Spot 3 beautiful things along the way.—Wakey Wakey. Regularly challenging our brain keep us alert and interesting. When we take notice of our surroundings we start to live life to the fullest.	✓	
Personalised Do	10	Based on behavioural questionnaire	WHAT ARE YOU EATING FOR? Back off from boredom, address your stress. Get busy, unwind, release your emotions so you only eat when you're hungry today.	✓	
System Message	3	Encouragements, tips, manage expectations	HEALTH TIP. Regular contact with friends and family is key to good mental and physical health. Connections give meaning and purpose to our lives, even when it is digitally.	✓	
Expander Do	3	Prompt user to explore new parts of personality, based on behavioural questionnaire	EXPANDER: It's NO Day today. Don't say yes when you really want to say no. Give no reason or excuse. Just say, 'Sorry, but the answer's no'.	✓	
Preventomics Messages	6	Template messages that use inputs from the nutritional recommendations of food to increase	PREVENTOMICS: Are you getting the right amount of {{.R1}} and {{.R2}} in your diet? Go online and find some interesting recipes to try at home. Do it now.	✓	
General Messages	24	Recommendations from the NHS and WHO on eating, eating out, exercise, check-ups, help and support, balanced diet	Eating a healthy, balanced diet is an important part of maintaining good health, and can help you feel your best. This means eating a wide variety of foods in the right proportions, and consuming the right amount of food and drink to achieve and maintain a healthy body weight.		✓

C, control; NHS, The National Health Service; PP, personalised plan; PREVENTOMICS, Empowering consumers to PREVENT diet-related diseases through OMICS sciences; WHO, World Health Organization.

Appendix 4.2: Productivity costs calculation

This appendix provides more information on the cost calculation of productivity loss. This explanation is based on information provided by Hoogendoorn et al. (281).

The costs of productivity loss were estimated based on SHARE data (245) for central European countries since the employment status in Denmark is comparable with those in central European countries (304,305).

Costs for long-term work loss were calculated using data on the percentage of people with a paid job (Table 4.2.1), the mean number of working hours per week (Table 4.2.1) and the probability of becoming unemployed (Table 4.2.2). The friction costs method, with additional input provided in Table 4.2.3, was applied in this process.

Table 4.2.1: Coefficient for the equation prediction probability to be employed at baseline†.

	Coefficients
Country	Central-European countries
Intercept	-14.6526***
Sex (female vs. male)	0.7523***
Age	-0.00861***
Age²	-0.3354***
Working hours per week	Males: 38, Females: 30

*** p<0.001; †Prob=exp(outcome_equation)/(1+exp(outcome_equation)).

Table 4.2.2: Coefficients for regression equation predicting the probability to become unemployed ‡.

Coefficient	Coefficients
Country	Central-European countries
Intercept	-2.7395***
Sex (Female=1)	0.09195**
Age (years, scaled) †	0.7042***
BMI (continuous)	0.01681***
Diabetes incidence (Yes=1)	-0.1404
Stroke incidence (Yes=1)	0.2981*
Heart attack incidence (Yes=1)	0.01624

† Age_scaled = as (age-mean[age])/std; where mean= =57.67046; std=6.064744
‡ Probability = exp(outcome_equation)/(1+exp(outcome_equation))
* significant at <0.05; **significant at <0.01; ***significant at <0.0001

The productivity costs for short-term working hours lost were calculated by multiplying the estimated annual number of working days lost (Central-European countries: without disease = 10 days, with disease = 15 days) with the reference price (see Table 4.2.3).

Table 4.2.3: Friction period (306) and reference price (307).

Friction period in days	Productivity cost per hour 2020
91.25	338 DKK

Appendix 4.3: Method used to calculate unrelated medical costs.

Unrelated medical costs were calculated by subtracting the related costs per capita for diabetes, IHD and stroke from the annual healthcare spending per capita by sex and age. This annual healthcare spending per capita by sex and age was calculated following several steps.

1. Information from the DYNAMO-HIA project (217,218) about the percentage of people with disability per age group, divided by sex (in year 2014), was used as a proxy for a certain distribution of the total healthcare costs over the Danish population.
2. The total healthcare expenditure of Denmark, in 2014 (333), which was 201,522 DKK in millions of units, was divided over de different age groups by sex, based on the defined distribution in step 1, In this way, we got a total expenditure per age group divided by sex.
3. The total healthcare expenditure per capita was calculated by dividing the total expenditure per age group divided by sex that was found in the second step, by the number of people in that certain age group divided by sex (217,218).
4. The total healthcare expenditure per capita was divided by 'last year of life' and 'other years of life' with the following formula in R, using R studio:

*sc <- as,matrix(R_file_data_female$ac,tot)/(1 + (as,matrix(R_file_data_female$r,i)-1)*R_file_data_female$mr)*
*dc <- as,matrix(R_file_data_female$r,i)*sc*

*sc <- as,matrix(R_file_data_male$ac,tot)/(1 + (as,matrix(R_file_data_male$r,i)-1)*R_file_data_male$mr)*
*dc <- as,matrix(R_file_data_male$r,i)*sc*

Hereby, 'ac,tot' is the same as total healthcare expenditure per capita as found in the third step, 'r,i' is the ratio of decedent/survivor as found in an article written by Kalseth et al. (334). It was assumed that this ratio could be applied in the Danish setting. 'Mr' is the overall mortality rate that was used from the DYNAMO_HIA study (217,218).

This resulted in a total healthcare expenditure per capita divided by last year of life and other years of life.

5. Prevalence data of diabetes, IHD and stroke were obtained from the DYNAMO-HIA study (217,218), as well as incidence data of MI and stroke, all divided by age and sex.
6. The prevalence/incidence data together with the disease related costs per capita, were used to calculate the related costs. These costs were subtracted from the total healthcare expenditure costs per capita, to finally get the total unrelated healthcare costs per capita per age group divided by sex.
7. These costs were converted to 2020 DKK using the Consumer price index (310).

Appendix 4.4: Non-medical costs calculation

Mokri et al. (244) applied a method that utilized the methodologies of van Baal et al. (335) and Kellerborg et al. (239) as a starting point to calculate non-medical costs. Due to constraints in data availability, adjustments were made by Mokri et al. (244) to the cost derivation. In our study, we adopted this methodology applied by Mokri et al. (244) to calculate the non-medical costs for Denmark. A summary of this approach will be presented in this appendix.

The costs were determined based on non-medical consumption per household equivalent (244). This involved adjusting household consumption to account for economies of scale within households in terms of consumption. In other words, as the household size grows, the marginal consumption by each additional member decreases, leading to a reduction in the costs of consumption per person in larger households (336). When applying the economies of scale concept to future non-medical costs, it implies that preventing a death in a single-person household would contribute to more future non-medical consumption compared to preventing a death in a multi-person household (247).

The following equation was used to estimate the average annual non-medical consumption by age, when a death in an average household is prevented:

$$nmc(a) = [hh\ equiv(a) \times h(a) \times w] + [hh\ equiv(a) \times (1 - h(a))]$$

'h' is the probability of a household having more than one adult
'hh equiv' is the annual non-medical consumption per household equivalent
'w' is the consumption share of a household member: 0.5 for an adult and 0.3 for a child

For this, we utilized aggregate-level data from Eurostat's Household Budget Surveys (308), focusing on the average household consumption corresponding to distinct age groups of the main breadwinner—categorized as less than 30 years, 30-44 years, 45-59 years, and 60 years or over. Components that were included in these data were all household purchases such as rent, food, clothing, and transport.

We estimated the average non-medical costs per household equivalent based on the age category of the breadwinner. These costs were adjusted for both the average household size and economies of scale within households, accounting for the first and second adults. To determine the likelihood of having more than one adult per household, we incorporated data from UK sources (244). A smoothing function was applied to interpolate the age profiles.

Appendix 4.5: Details on probabilistic sensitivity analyses from Hoogendoorn et al. 2023 (281)

To incorporate the inherent uncertainty in input parameters and its impact on model outcomes, a probabilistic sensitivity analysis (PSA) was conducted. The PSA encompassed uncertainty surrounding relative risks (RRs) associated with body mass index (BMI) and its relationship with all-cause mortality and obesity-related diseases, as well as cost uncertainties. Other parameters were held constant during the analysis, which was because of several reasons. First and foremost, it was anticipated that the results would predominantly depend on relative risks, making them the primary focus of the PSA. Second, introducing uncertainty for parameters such as prevalence, incidence, BMI in the population, mortality, etc., proved challenging due to their interdependence. Altering one of these parameters, like observed BMI, inherently affects others, such as disease prevalence and mortality. Consequently, separate adjustments become impractical. Third, incorporating uncertainties for utilities posed additional challenges, as they are age- and sex-dependent, requiring percentage adjustments for each age and sex. Finally, while uncertainties for utility decrements could have been added, the lack of data on the magnitude of uncertainty led us to forgo this inclusion. Additionally, it was expected that including uncertainty around these decrements would have impacted the results minimally.

For the RRs associated with BMI and all-cause mortality, uncertainty intervals of 11 different BMI values from Aune et al. (208) were used. Ten random values were drawn from the intervals around the relative risks for each reported value of BMI, assuming a normal distribution. Using second-degree polynomial regression, a model was estimated with RR as the outcome and BMI as the predictor, based on the mean RRs and surrounding uncertainty. In the PSA, uncertainty was derived from the uncertainty around the coefficients in the estimated model and random draws for all coefficients were made by considering their covariance. Results were estimated separately for males and females.

A similar approach was used for RRs reflecting the association between BMI and obesity-related diseases. The Global Burden of Disease Study (216) provided RRs for 12 age groups including their uncertainty intervals. Random draws (10 per observation) around each reported RR were taken and were assumed to follow a normal distribution. Subsequently, a linear model was estimated based on the reported RRs and surrounded uncertainty, using age as the predictor and RR as outcome. For the PSA, random draws for the coefficients were made while considering covariance.

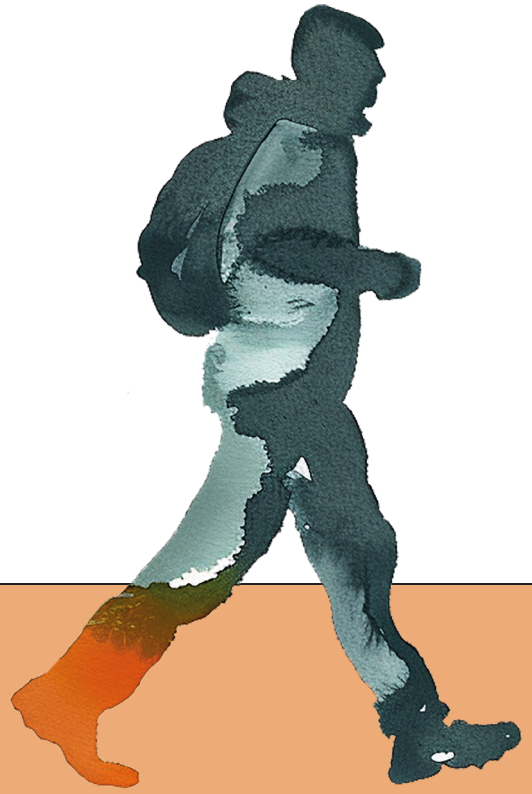
Due to the absence of available data on cost uncertainty, a standard error of 20% of the mean value was assumed for all cost estimates. A gamma distribution was applied for cost uncertainty. The effectiveness estimates from the trial and intervention costs were assumed to follow a normal distribution.

Appendix 4.6: Results of the scenario analysis

Table 4.6.1: QALYs and costs of a scenario analysis in which non-medical costs and unrelated medical costs were excluded.

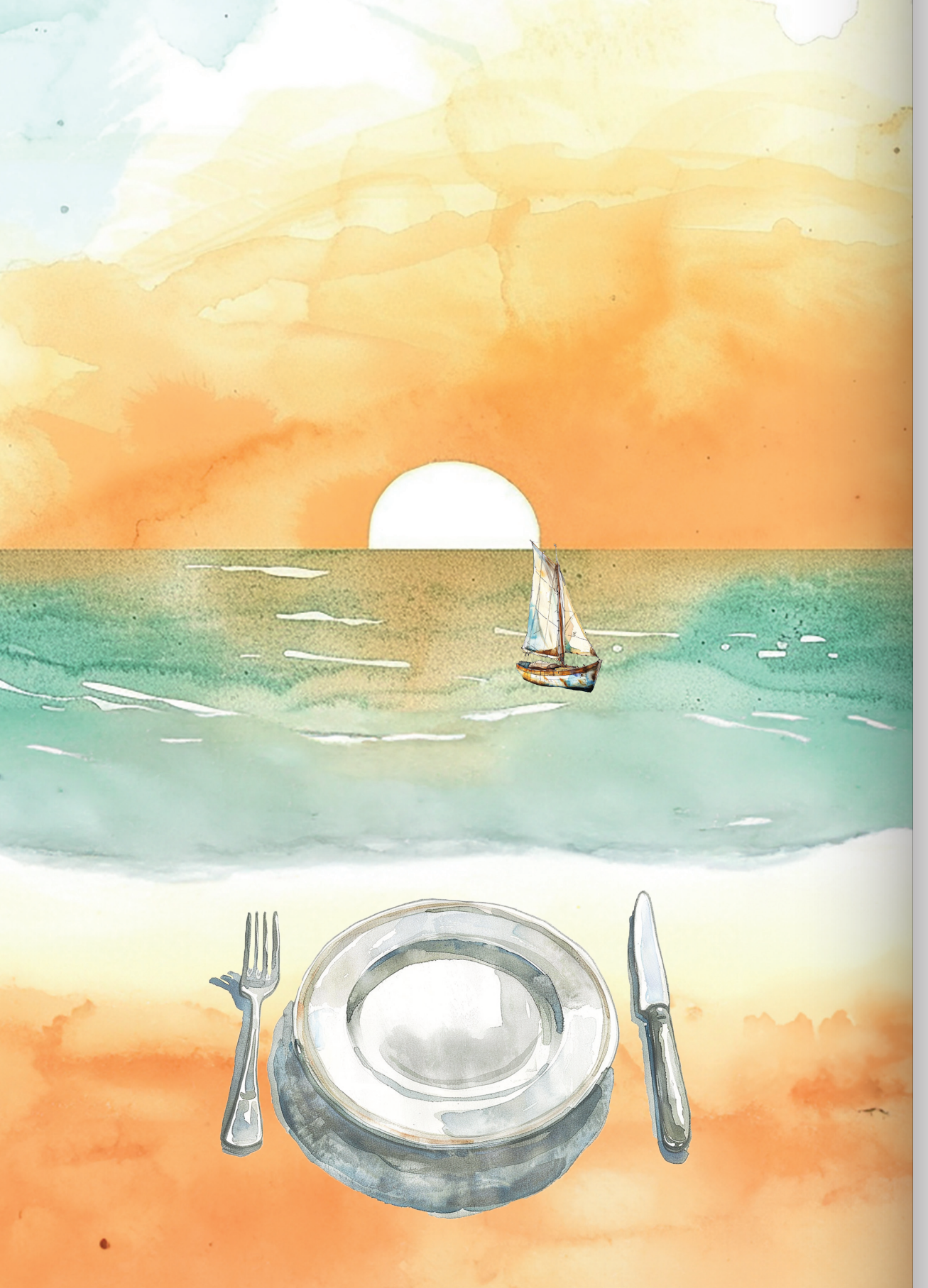
	Discounted at 4%			Undiscounted		
	PP	Control	Difference	PP	Control	Difference
Effects						
QALYs	15.117	15.106	0.011	28.483	28.464	0.019
Costs (in 2020 € (DKK))						
Diabetes	18,118 (135,305)	18,193 (135,864)	-75 (-559)	46,769 (349,272)	46,926 (350,445)	-157 (-1,173)
IHD	2,910 (21,732)	2,916 (21,774)	-6 (-43)	7,219 (53,915)	7,230 (53,997)	-11 (-82)
Stroke	3,642 (27,199)	3,649 (27,252)	-7 (-53)	10,775 (80,465)	10,791 (80,586)	-16 (-121)
Unrelated	-	-	-	-	-	-
Non-medical	-	-	-	-	-	-
Intervention	7,402 (55,277)	5,653 (42,215)	1,749 (13,062)	7,402 (55,277)	5,653 (42,215)	1,749 (13,062)
Informal care	5,581 (41,680)	5,582 (41,683)	0 (-3)	16,169 (120,753)	16,164 (120,713)	5 (41)
Productivity	17,234 (128,703)	17,236 (128,772)	-3 (-19)	24,668 (184,221)	24,670 (184,240)	-2 (-18)
TOTAL	55,558 (414,908)	53,904 (402,560)	1,658 (12,385)	113,996 (851,329)	112,433 (839,657)	1,568 (11,708)
ICUR	***156,173 (1,166,309)***			***84,076 (627,880)***		

DKK Danish Krone, *ICUR* incremental cost-utility ratio, *IHD* Ischemic heart disease, *PP* Personalized Plan, *QALYs*, quality-adjusted life years.



Part 3

Transition: to a broader health technology assessment perspective



Chapter 7

Preferences and willingness to pay for personalized nutrition interventions: Discrete choice experiments in Europe and the United States

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ABSTRACT

Objectives

This study gives insight into what intervention-related factors are crucial for using personalized nutrition (PN) interventions, as well as what the general population is willing to pay for PN.

Methods

This was done by focusing on two different types of PN (i.e., PN advice and personalized meals) in two discrete choice experiments (DCEs). The DCEs were conducted in four European countries and the United States, including at least 500 respondents per country aged 18-65 years. Panel mixed multinomial logit models were used to evaluate the preferences.

Results

Results show that for both types of PN in all countries, the total expenditure on nutrition was the most crucial factor when choosing a PN intervention. The participation rate for specific hypothetical scenario's varied but was considered high overall (maximum 81% for 'PN advice' and 87% for 'personalized meals' in Spain). Moreover, highest willingness to pay estimates were found for six kilograms of weight loss. For example, Polish respondents were willing to spend an extra 25.78 euros per week for 'personalized meals' for a 4-month period to lose six kilograms. Our models showed preference heterogeneity between, but also within, the different countries.

Conclusions

In conclusion, this study showed that people seem willing to pay for and participate in PN interventions. Since PN interventions may improve health outcomes, policymakers should consider subsidizing some of the costs, financially incentivizing PN interventions or introducing commitment lotteries to encourage uptake. More research is needed to study heterogeneity in preferences.

INTRODUCTION

Globally, 41 million people die each year from noncommunicable diseases (NCDs), which is equivalent to 74% of all deaths (2). Many types of NCDs, such as cardiovascular diseases, cancers, and diabetes, occur because of a combination of genetic, physiological, environmental, and behavioral factors. Behavioral factors are oftentimes modifiable and include tobacco use, alcohol use, physical activity, and an unhealthy diet, which increase the risk of NCDs and thereby increase the number of deaths. For example, there are yearly 1.8 million deaths attributed to excess salt/sodium intake, since over usage could lead to high blood pressure and cardiovascular disease (385). Among most NCDs, a diet is a common risk factor and therefore attracts attention and effort to find effective strategies for providing healthy food (386). One of these strategies may be personalized nutrition (PN).

PN has no agreed definition, but it can be seen as an approach that uses individual characteristics, such as genetic, phenotypic, medical, nutritional, and other relevant information to develop targeted nutritional advice, products, or services (23) with the overall goal to preserve or improve health. Since advice, products or services are more relevant for a specific person when personalized, this can in turn lead to a higher compliance to a specific PN intervention (372,387). This personalized way of providing nutrition interventions has been shown in previous research to be more effective than generic nutrition interventions, although there is not yet consistency in evidence of effectiveness (36,38,387).

Several studies have demonstrated that there is a high degree of interest in PN, and that there might even be a market for PN (388,389). PN is explained by Ordovas et al. (23) who make a distinction between a biological/medical basis (i.e., different responses to foods because of genotypic or phenotypic characteristics) and the behavioral/psychological basis of nutrition (390). Combining these two creates a 'high level' of personalization of nutrition. New interventions developed in different projects, such as PREVENTOMICS (Empowering consumers to PREVENT diet-related diseases through OMICS sciences, Horizon 2020: No.818318), can be viewed as PN with both biological/medical information and behavioral/psychological information (i.e., high level of PN) (8). During the PREVENTOMICS project a platform was developed, including a decision support system, which was integrated into three interventional studies. The focus of two of these studies was on PN advice and one of these studies delivered personalized meals. Moreover, a behavioral change program was included in all of the interventional studies (see website for more information (41)). The PREVENTOMICS project showed promising results of effectiveness but with uncertainty surrounding the effects (47,391). Besides the effectiveness, there might be several intervention-related factors that affect individual's willingness and ability to use a PN intervention. Gaining insights in what factors of different high-level PN interventions individuals found important is relevant for the developers and designers of PN interventions (392). With this, a PN intervention can be tailored to the needs of an individual, which in turn might lead to more satisfaction, better uptake, better health, and more efficient interventions (393).

There are methods available to quantify people's preferences regarding different characteristics of interventions (64,65). In this, 'preferences' could be defined as 'qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alterative health interventions' (394). One method to elicit individuals' preferences that is increasingly being used in healthcare and public health (395) and often used in food research as well (63) is a discrete choice experiment (DCE). In a DCE, respondents are asked to state their preferences by evaluating several hypothetical interventions, which are shown to respondents in a series of questions called choice tasks (64,65). These interventions have several characteristics (i.e., attributes) that vary (i.e., attribute levels). It is possible to study the relative importance of attributes and levels to one another with statistical methods. These methods underline the random utility theory in which each option that is considered has latent utility and the choice alternative with the greatest utility to the respondent will be chosen (66–69). Moreover, statistical methods can be used to elicit marginal rates of substitution such as the willingness to pay (WTP) (66); which reflects the amount users would be willing to pay in order to gain something else such as health. Since users of PN interventions are expected to pay at least a part of the intervention costs out-of-pocket, it is important to estimate this WTP (68,70). Although the aim of this study is not to explain heterogeneity in preferences by identifying factors that influence preferences, it is crucial to explore how WTP varies across income levels. This exploration is motivated by previous research suggesting that [1] price might be an important factor for (dis)utility associated with meal choices (396) and could therefore potentially be a barrier to participate in PN interventions and [2] income could be correlated to this (396). This information can be valuable when making decisions about the implementation and reimbursement of PN interventions. Moreover, it is important to know if the preferences and WTP differ between countries, since culture differences might lead to different flavors, meal patterns, meal cycles (397) and thereby potential differences in preferences about PN.

To our knowledge, no preference study has ever investigated people's preferences regarding the characteristics of different types of high-level PN interventions and the WTP of PN interventions. However, preferences of respondents for specific interventions will be increasingly important for health technology assessment bodies as supportive evidence (60). Therefore, the aim of this study was to determine which intervention-related factors are crucial for people when deciding to participate in PN interventions as well as how much the general population in Europe and the United States (US) is willing to pay for PN interventions. Additionally, we aimed to calculate the population level participation rate for different hypothetical PN interventions and to investigate if and to what extent the outcomes differ between countries (while accounting for heterogeneity in preferences of respondents within and between countries). The PN interventions that we studied were 'PN advice' and 'personalized meals'. Based on the outcomes, recommendations can be made on what characteristics of PN interventions would most likely be preferred by the potential users. These recommendations can be considered when developing PN interventions to prevent NCDs, thus increasing their reach, and hence their public health benefit.

METHODS

Discrete choice experiment

This study used an online questionnaire containing two different DCE's to elicit people's preferences for attributes of PN interventions. These two DCE's consisted of two hypothetical PN interventions primarily based on the interventional studies from the PREVENTOMICS project: DCE1: 'PN advice' and DCE2: 'personalized meals' (8,41).

Study sample and recruitment

For the DCEs in this study, a study sample of individuals aged 18-65 years were recruited from the general population representing the US and all wind directions of Europe: the Netherlands (west), the United Kingdom (UK) (north), Spain (south) and Poland (east) (398). These countries were chosen for different reasons. First, literature showed that central/northern European countries have different meal patterns than Mediterranean countries, which involves a reason to include these variety of European countries (399). Second, the US was included as well, since this might show interesting differences due to differences in food consumption patterns and culture (397,400). The general population was chosen since PN might be useful for preserving health and preventing diseases.

Respondents were required to provide informed consent to participate in the study and were recruited via a commercial survey sampling company Dynata, Rotterdam, Netherlands. These respondents received a small financial compensation when the questionnaire was completed. Data was collected in the UK and in the Netherlands in May 2022 and in Poland, Spain, and the US in September 2022. Recruitment in each country was continued until at least 500 respondents completed the questionnaire. The study was approved by the internal ethical review board of the Erasmus School of Health Policy & Management [IRB 20-15].

Case study, attributes, and levels

In this study, two different DCEs involving two different types of PN interventions were performed. These types were [1] PN advice and [2] personalized meals. These types were primarily chosen because of interventional studies that took place as part of the PREVENTOMICS project. Moreover, a recent literature review of the cost-effectiveness of PN interventions, showed that PN advice was the most frequently assessed type of PN intervention when cost and effects of PN were investigated (280).

For both DCEs, attributes and levels were derived (independently for both DCEs) by several consecutive steps. These included a literature review, focus group studies with the general population and expert interviews. First, a list of different characteristics of PN interventions was compiled, following previous published literature (36,48,280,401,402). This resulted in the first draft of attributes and levels. Second, to ensure that all different characteristics of PN interventions were included, three focus group studies were conducted with a total of 18 participants from the Netherlands. An additional aim of the focus groups was to gain

information about the different levels for the attributes. The focus group studies were conducted following the guideline of Krueger (403). We had no reason to believe that other important attributes had come up if focus groups were conducted in more countries. See Appendix 7.1 for more details about the focus groups methods and a summary of the results. Third, the attributes and levels created were presented to different nutrition intervention experts (i.e., different partners in the PREVENTOMICS project) and choice modeling experts, during a meeting with the Erasmus Choice Modeling Centre. This was done to ensure that the attributes and levels were clinically relevant, suited the PREVENTOMICS project and fulfilled the properties of a rigorous DCE. Lastly, they were finalized by the research team. These three steps resulted in six different attributes with different levels for the two DCEs. Tables 7.1 and 7.2 show the attributes and levels.

Table 7.1: Attributes and levels of discrete choice experiment 1 (DCE1) 'PN advice' in the Netherlands.[a]

Attribute: *explanation*	**Attribute Level**
Type of personalized nutrition advic*e: given via an app on people's mobile phone.*	Advice on recipes via app Advice on food products via app
Number of dietitian appointments*: face-to-face or online consultations for extra support/monitoring.*	0 per month 1 per month 2 per month 3 per month
Number of behavioral reminders*: personalized messages sent via an app to motivate people for stepping out of the comfort zone and to try new behaviors that contribute to a healthy lifestyle.*	0 per week 1 per week 3 per week 1 per day
Total expenditure on nutrition*: amount people spend on everything related to nutrition and consisted of two components: [1] the attribute level (i.e., the extra amount people spend because of the PN intervention) and [2] respondents' current expenditure. The summed amount of these two components was shown to the respondent.*	0 euros per week 31 euros per week 63 euros per week 94 euros per week
Use of time*: the time people spend compared to their current eating pattern, by getting PN advice (e.g., time for blood sampling or dietitian appointments).*	5 minutes more per day 15 minutes more per day 30 minutes more per day 60 minutes more per day
Expected outcomes*: health outcomes of the intervention.*	Longer life expectancy and weight loss of up to 0 kilograms after 4 months Longer life expectancy and weight loss of up to 2 kilograms after 4 months Longer life expectancy and weight loss of up to 4 kilograms after 4 months Longer life expectancy and weight loss of up to 6 kilograms after 4 months

Note: [a] The attributes and levels are the same for all other countries, but 'total expenditure on nutrition' was converted with the purchasing power parity to relevant currencies and amounts.

Table 7.2: Attributes and levels discrete choice experiment 2 (DCE2) 'personalized meals' in the Netherlands.[a]

Attribute	**Attribute Level**
Meals provided	Personalized dinner Personalized lunch and dinner Personalized breakfast and dinner Personalized breakfast, lunch, and dinner
Number of dietitian appointments	0 per month 1 per month 2 per month 3 per month
Number of behavioral reminders	0 per week 1 per week 3 per week 1 per day
Total expenditure on nutrition	0 euros per week 81 euros per week 163 euros per week 244 euros per week
Use of time	5 minutes more per day 15 minutes more per day 30 minutes more per day 60 minutes more per day
Expected outcomes	Longer life expectancy and weight loss of up to 0 kilograms after 4 months Longer life expectancy and weight loss of up to 2 kilograms after 4 months Longer life expectancy and weight loss of up to 4 kilograms after 4 months Longer life expectancy and weight loss of up to 6 kilograms after 4 months

Note: [a] The attributes and levels are the same for all other countries, but 'total expenditure on nutrition' was converted with the purchasing power parity to relevant currencies and amounts.

DCE design and questionnaire

The questionnaire that included the two DCEs was developed and designed following good research practices (64,395). A draft questionnaire was assessed in a pre-testing session with ten respondents in the Netherlands. Furthermore, seven think-aloud sessions were held to obtain more insight into how people approached answering the questionnaire (64). This draft questionnaire was comparable to the final questionnaire, as respondents indicated that the questionnaire was clear, and that the length was manageable. Only minor changes were made in the formulation of attributes, levels, and some questions. After pre-testing, the questionnaire was translated into English by the researchers and a pilot with the final questionnaire was done in the Netherlands and the UK with approximately 10% of the total study sample in the Netherlands and the UK. The set-up of the questionnaire is explained later in this paragraph.

In reference to the DCEs included in this questionnaire, it was not possible to present all combinations of attributes and levels to the respondent, since this would result in an unfeasible

number of combinations of alternatives. Therefore, a subset of alternatives was selected using a Bayesian D-efficient design, which is increasingly used in food DCEs (63), generated with NGene 1.2.1 software (404,405). For the pilot study beta priors were based on best guesses with uniform distributions. These distributions and beta priors were updated based on the pilot data in the Dutch setting (n=52) (405). Attributes that showed significance, were updated accordingly assuming a normal distribution, other attributes were updated while maintaining uniform distributions. In the other four countries, the same updated design (i.e., updated priors) as in the Netherlands was used to eliminate possible between-country differences in preference outcome resulting from the design (406). No other changes were made to the questionnaire after the pilot study and data collection was completed in the Netherlands and the UK. Partners from the PREVENTOMICS project translated the questionnaires to Polish and Spanish using backward and forward translation, after which the pilot and final data collection was done in those remaining countries including the US.

Both DCEs consisted of 24 choice tasks that were divided into three blocks of eight choice tasks per block, each containing two alternatives. This was done to reduce the burden for the respondent. The design forced respondents to choose between the two alternatives (i.e., types of PN interventions), but after each choice task, respondents were asked whether they would actually choose the intervention they had selected or if they would rather choose their own current eating pattern (i.e., opt-out) (407). This opt-out option was included as in real life people may also want to stick by their current eating pattern and not want to choose a PN intervention (408). The opt-out showed people's actual current eating pattern (based on previous asked questions), because literature shows that respondents use their current choices as a reference for ranking hypothetical alternatives (409). An example of a choice task for 'PN advice' can be found in Figures 7.1 and 7.2. The DCE for 'personalized meals' had the same form as 'PN advice'.

	Personalised nutrition advice (1)	Personalised nutrition advice (2)
Type of personalised nutrition advice	Advice on recipes via app	Advice on food products via app
Number of dietitian appointments	1 per month	3 per month
Number of behavioural reminders	1 per day	1 per week
Total expenditure on nutrition	50 pounds per week	107 pounds per week
Use of time	5 minutes more per day	30 minutes more per day
Expected outcomes	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	Longer life expectancy and weight loss of up to 2 kilograms after 4 months

Figure 7.1: Example of a choice task of 'PN advice' in the UK. Respondents had to choose between these alternatives and select their preference.

		Personalised nutrition advice (2)	Your current eating pattern
Type of personalised nutrition advice	Advice on recipes via app	Advice on food products via app	No personalised nutrition advice via app
Number of dietitian appointments	1 per month	3 per month	0 per month
Number of behavioural reminders	1 per day	1 per week	No (personalised) reminders
Total expenditure on nutrition	50 pounds per week	107 pounds per week	50 pounds per week
Use of time	5 minutes more per day	30 minutes more per day	0 minutes less/more per day
Expected outcomes	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	Longer life expectancy and weight loss of up to 2 kilograms after 4 months	No longer life expectancy and no weight loss after 4 months

Figure 7.2: Example of a choice task of 'PN advice' in the UK. Respondents were shown the chosen PN intervention from the first step and were asked to compare this with their current eating pattern and select their preference.

Before the choice tasks were shown to the respondents, the questionnaire started with an introductory text and the request for informed consent. The remainder of the questionnaire was divided into seven sections. The first section contained questions regarding some general respondent characteristics, such as age, gender, height, and weight. The second section included questions about respondents' current eating style, by asking several questions about the use of (personalized) nutrition interventions and expenditure behavior. The aim of these questions was twofold: a) to get more insight in people's use of nutrition interventions and expenditure behavior and b) to use the answers to these questions as input for the opt-out option in the DCEs. Third, people were given a detailed explanation of all attributes and levels, followed by instructions on how to complete a choice task with an example. Fourth, the respondents were shown the first eight choice tasks ('PN advice'), where every choice task started with the question: 'Imagine having the choice between two different personalized nutrition advice. Which of the options below [1 or 2] would you prefer?'. In the next step, the following question was asked: 'Suppose you have to choose between your previous choice for personalized nutrition advice [1] and your current eating pattern. Which option would you prefer? Personalized nutrition advice [1] or your current eating pattern?'. The fifth section contained some general questions, such as marital status, household size, nationality, educational status, work, and income. Sixth, respondents were shown another extensive explanation about the meaning of the next attributes and levels and continued with the next eight choice tasks ('personalized meals'), where every choice task started with the question: 'Imagine having the choice between two different personalized meal interventions. Which of the options below [1 or 2] would you prefer?'. Followed by asking them again to choose between their previous choice and their current eating pattern. The sixth section contained some lifestyle related questions based on questions set up by Dieteren et al. (410) where we asked respondents about their experiences with health, allergy, eating habits, exercise patterns and health goals (410). Finally, we closed with questions about the perceived difficulty of the questionnaire and the option for the respondent to provide feedback or ask questions

about the study. The questionnaire was designed using Sawtooth Software Lighthouse Studio 9.8.0.

Statistical analyses

The choices that respondents made in the DCEs were used to analyze which trade-offs respondents were willing to make regarding different PN intervention attributes. The data were analyzed separately in every country in both DCEs. Data was handled as if respondents had three options to choose from.

As a starting point for model specification, a main effects multinomial logit model (MNL) was used. We tested for linearity of the numeric levels and included two alternative specific constants to correct for [1] the first presented alternative (left bias) and [2] the last presented alternative (the opt-out) (i.e., left-right bias). Attributes were considered categorical if in at least one country the slopes of the levels of one attribute were unequal (411). This was the case for all attributes in both DCEs and so these attributes were dummy coded. However, 'the total expenditure on nutrition' was analyzed as a continuous variable since this allows us to calculate respondents' marginal WTP (412). The alternative specific constant for left bias was excluded in the end, since in both DCEs this constant was not significant ($p > 0.05$) in any country. Finally, panel mixed multinomial logit (MIXL) models were used to allow preference heterogeneity and to adjust for the multilevel structure of the data (each respondent answered eight choice tasks) (413). Based on the significance of the estimates of the standard deviations (SDs), it was decided which attributes to include as random parameters (with normal distribution) due to significant preference heterogeneity ($p < 0.05$). This was done for each country and DCE separately and attributes were included as random if the SDs of at least one level of the attribute was statistically significant ($p < 0.05$). The equations for the final main effect models that were used to estimate the utility of either 'PN advice' or 'personalized meals' can be found in Appendix 7.2.

Parameter estimates (β) from the analyses were used to indicate the relative importance of attributes and their levels. If the coefficients were statistically significant at alpha=0.05 this indicated that respondents considered the attribute important in making their choices concerning PN. The sign of the parameter estimates reflects whether the attribute level had a negative or positive effect on utility. The size of these coefficients was further used to examine the relative importance of the attributes. The relative importance of attributes was assessed by first taking the difference between the most and least desirable attribute level in each attribute. Second, this difference was divided by the sum of differences of all attributes (414). The larger this value, the larger the relative importance of an attribute. Moreover, we calculated how many respondents always chose the opt-out option, and how many respondents who chose a PN intervention in all choice tasks, always chose the PN intervention with the lowest cost level. These calculations were performed for each country separately, including the distinction between 'PN advice' and 'personalized meals'.

Moreover, as described earlier in this section, the coefficients were used for calculating the WTP (68,412). This was done to calculate the amount of money an individual is willing to spend to lose weight. The 'total expenditure on nutrition' and 'expected outcomes' were used as a proxy for this. As stated before (section 'case study, attributes, and levels'), 'the total expenditure on nutrition' consisted of two components, of which the attribute level was used for WTP calculations. The WTP can been seen as the ratio of the attribute coefficients of 'expected outcomes' to the cost coefficient (412). Since the 'expected outcome' is not linear, the WTP is consequently not fixed in each country and instead differs per change in level of the 'expected outcome'. The difference in individual coefficients between two levels was thus divided by the individual coefficient of 'total expenditure on nutrition' to calculate the WTP. Individual coefficients were used since both attributes were included as random parameters in the analyses (67,68). Additionally, since only one component (i.e., the attribute level) was used as a proxy for the cost component, we studied whether the WTP varied when the other component (i.e., current expenditure on nutrition) was low or high. A distinction between low and high current expenditure was based on the median, where respondents with an expenditure above the median were labeled as 'high'.

To calculate the uptake or participation rate for the different PN interventions, four alternative scenarios were chosen. This was done for [1] the least preferred scenario, [2] the most preferred scenario, and [3-4] PREVENTOMICS interventions. The last two scenarios included attribute levels that were assumed to resemble the interventions studied during the PREVENTOMICS project. These scenarios were all compared to having no PN intervention, and thus with the current eating pattern. Uptake was predicted by taking the exponent of the utility for the intervention scenario under evaluation divided by the sum of the intervention scenario utility's exponent and the no treatment utility's exponent (66). Again, the choice probabilities could not be calculated directly since attributes were included as random parameters, and therefore individual estimates were used. The mean participation rates of all respondents were calculated by taking the average of all participation rate probabilities.

Since we compared the attribute level estimates of five countries, the role of the scale parameter needs to be considered (415). This is because the coefficients that are estimated in models are a ratio of the true parameter estimates and a scale parameter (i.e., inverse variance) (415,416). However, since variances might differ between countries (i.e., data sets), the attribute level estimates cannot be compared directly between countries before scale factor differences (differences in variance) between the models are ruled out. We used the Swait and Louviere test for this purpose. Details about the applied Swait and Louviere test can be found in the study by Veldwijk et al. (416). All analyses were done using Stata 17 software.

RESULTS

Respondents' characteristics

In total, 513 respondents completed the questionnaire in the Netherlands, 525 in the UK, 516 in the US, 501 in Spain and 501 in Poland after the inclusion criteria were met and informed consent was provided. The respondents had a median age ranging from 39 years in Poland to 48 years in the Netherlands. In all countries, there were slightly more females than males. The median body mass index (BMI) of respondents in the Netherlands, the UK, Spain, and Poland was very close to being overweight (BMI >25 kg/m2) and the median BMI of respondents in the US just passed the BMI minimum of overweight; this is supported by the percentages of respondents in the overweight and obese weight category (417). Most of the respondents in all countries rated their health as 'very good' or 'good' and the Netherlands had the biggest proportion of respondents that indicated having a healthy diet (40.2%) and to be physical active (47.8%). Lastly, approximately one-quarter to one-third of respondents reported having a chronic disease, ranging from 24.4 percent in the UK to 35.3 percent in Poland. See Appendix 7.3 for more details about the respondents' characteristics.

Preference heterogeneity and relative importance

Table 7.3 shows the results of the panel MIXL model for 'PN advice' stratified by the countries. The cost attribute (i.e., total expenditure on nutrition) showed statistically significant estimates in similar direction in all countries; meaning that all respondents preferred lower cost levels over higher cost levels. The negative coefficient of the opt-out option (i.e., current eating style) means that people a priori preferred one of the 'PN advice' options over their current eating pattern (i.e., the opt-out), all else being equal. Moreover, all respondents preferred a longer life expectancy and a weight loss in kilograms after four months over zero kilograms of weight loss. These estimates were statistically significant in all countries. Significant preference heterogeneity was shown for the cost attribute, the expected outcomes, and the opt-out option as can be seen by the significant SDs reported for these attributes (levels). Additionally, preference heterogeneity was shown for the behavioral reminder attribute in the UK, the US and Spain and for the use of time attribute in the Netherlands and Spain and preference heterogeneity was shown for the number of dietitian appointments in the Netherlands.

Table 7.4 shows the results of the panel MIXL model for 'personalized meals', stratified by the countries. The cost attribute (i.e., total expenditure on nutrition) showed here statistically significant estimates in similar direction in all countries as well. The opt-out indicated that people preferred one of the 'personalized meal' options over their current eating pattern. Moreover, the attribute 'expected outcomes' showed that people preferred kilograms of weight loss over no weight loss. Preference heterogeneity was found in all countries in the cost attribute and the number of dietitian appointments.

The relative importance of the attributes for 'PN advice' is shown in Figure 7.3. Relative to other attributes, the total expenditure on nutrition was the most important attribute, followed

by the expected outcomes. In the Netherlands, the US, Spain, and Poland, the type of PN advice was the least important attribute, while in the UK this was the number of behavioral reminders. Figure 7.4 shows the relative importance of the attributes for 'personalized meals'. Relative to other attributes, the total expenditure on nutrition was also found here to be the most important attribute in all countries. This was followed by the expected outcomes, except for the Netherlands, where relative to other attributes, the number of dietitian appointments was the second most important attribute. The number of behavioral reminders was the least important relative to other attributes in the Netherlands and the US. 'Meals provided' was the least important in the UK and 'Use of time' in Spain and Poland.

The percentage of people that always chose their current eating style (i.e., opt-out) instead of 'PN advice' was 13.3% in the Netherlands, 9.7% in UK, 9.7% in US, 6.0% in Spain, and 11.0% in Poland. On the other hand, the percentage of people that always chose 'PN advice' and always preferred 'PN advice' with the lowest cost level (i.e., dominant decision-making on cost) was 0.8% in the Netherlands, 1.0% in UK, 0.6% in US, 2.6% in Spain, and 1.0% in Poland. For 'personalized meals' these percentages were quite comparable. The percentage of people that always chose their current eating style was 9.2% in the Netherlands, 8.2% in UK, 7.2% in US, 4.8% in Spain, and 7.2% in Poland. Moreover, the percentage of people that always chose for 'personalized meals' with the lowest cost level, was 1.9% in the Netherlands, 1.0% in UK, 1.4% in US, 2.2% in Spain, and 1.6% in Poland. Details on these results can be found in Appendix 7.4.

Table 7.3: Preferences for PN advice interventions (DCE1) based on a panel MIXL stratified by country.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Constant (opt-out)		-0.774**	0.187	-0.796**	0.157	-0.416*	0.166	-1.079**	0.188	-0.458*	0.183
Type of personalized nutrition advice	Advice on recipes via app (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	Advice food products via app	-0.015	0.069	-0.104	0.058	0.023	0.061	0.110	0.062	0.005	0.064
Number of dietitian appointments	0 per month (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	1 per month	0.083	0.109	0.041	0.086	-0.024	0.089	0.290**	0.093	0.263**	0.094
	2 per month	0.011	0.107	0.060	0.090	-0.195*	0.093	0.011	0.096	0.050	0.098
	3 per month	-0.170	0.097	-0.089	0.083	-0.286**	0.088	0.036	0.091	-0.001	0.091
Number of behavioral reminders	0 per week (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	1 per week	0.130	0.097	0.004	0.085	-0.067	0.092	0.252**	0.091	0.204*	0.090
	3 per week	0.056	0.098	0.065	0.082	0.145	0.086	0.234**	0.088	0.208*	0.091
	1 per day	0.239*	0.102	0.059	0.084	0.239**	0.087	0.300**	0.092	0.238*	0.094
Total expenditure on nutrition		-0.055**	0.004	-0.035**	0.003	-0.018**	0.002	-0.040**	0.003	-0.015**	0.001

Table 7.3: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Use of time	5 minutes more per day (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	15 minutes more per day	-0.173	0.105	-0.090	0.086	0.158	0.089	-0.078	0.093	-0.099	0.093
	30 minutes more per day	-0.207*	0.091	-0.074	0.078	0.122	0.082	0.030	0.083	-0.236**	0.085
	60 minutes more per day	-0.627**	0.111	-0.258**	0.093	-0.128	0.100	-0.328**	0.106	-0.397**	0.104

Table 7.3: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Expected outcomes	Longer life expectancy and weight loss of up to 0 kilograms after 4 months (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	Longer life expectancy and weight loss of up to 2 kilograms after 4 months	0.509**	0.107	0.097	0.087	0.254**	0.096	0.456**	0.097	0.568**	0.101
	Longer life expectancy and weight loss of up to 4 kilograms after 4 months	0.777**	0.095	0.368**	0.078	0.603**	0.089	0.672**	0.087	0.916**	0.089
	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	0.779**	0.108	0.465**	0.093	0.788**	0.106	0.897**	0.105	1.037**	0.108
SD											
Constant (opt-out)		2.513**	0.151	2.102**	0.124	2.187**	0.135	2.538**	0.162	2.517**	0.152

Table 7.3: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Type of personalized nutrition advice	Advice on recipes via app (ref)										
	Advice food products via app										
Number of dietitian appointments	0 per month (ref)	0.000	x								
	1 per month	-0.624**	0.215								
	2 per month	0.084	0.279								
	3 per month	-0.076	0.280								
Number of behavioral reminders	0 per week (ref)			0.000	x	0.000	x	0.000	x		
	1 per week			-0.392*	0.178	-0.516**	0.171	-0.434*	0.183		
	3 per week			-0.012	0.197	0.276	0.283	0.026	0.234		
	1 per day			0.061	0.228	-0.029	0.202	-0.095	0.283		
Total expenditure on nutrition		0.051**	0.003	-0.041**	0.003	0.025**	0.002	-0.045**	0.003	0.016**	0.001
Use of time	5 minutes more per day (ref)	0.000	x					0.000	x		
	15 minutes more per day	-0.650**	0.161					0.337	0.241		
	30 minutes more per day	-0.065	0.232					0.034	0.192		
	60 minutes more per day	-0.080	0.242					0.488**	0.177		

Table 7.3: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Expected outcomes	Longer life expectancy and weight loss of up to 0 kilograms after 4 months (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	Longer life expectancy and weight loss of up to 2 kilograms after 4 months	0.395	0.257	0.059	0.191	0.615**	0.169	0.544**	0.189	0.482*	0.225
	Longer life expectancy and weight loss of up to 4 kilograms after 4 months	-0.053	0.217	0.007	0.217	0.668**	0.144	-0.335	0.233	0.291	0.240
	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	0.708**	0.159	0.730**	0.132	1.123**	0.134	0.959**	0.142	0.963**	0.140

* Significant at P < 0.05. ** Significant at P < 0.01

Table 7.4: Preferences for personalized meals (DCE2) based on a panel MIXL stratified by country.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Constant (opt-out)		-2.250**	0.244	-1.325**	0.192	-1.184**	0.189	-1.712**	0.211	-1.081**	0.194
Meals provided	Personalized dinner	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	Personalized lunch and dinner	0.074	0.116	0.183	0.099	0.069	0.094	0.367**	0.104	0.151	0.099
	Personalized breakfast and dinner	-0.004	0.128	0.080	0.116	0.132	0.106	0.179	0.114	0.133	0.105
	Personalized breakfast, lunch, and dinner	-0.347**	0.117	0.085	0.098	-0.011	0.095	0.355**	0.105	-0.044	0.098
Number of dietitian appointments	0 per month (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	1 per month	-0.604**	0.146	-0.382**	0.124	-0.123	0.108	-0.219	0.113	-0.007	0.104
	2 per month	0.126	0.110	0.026	0.095	-0.043	0.092	0.145	0.097	0.134	0.094
	3 per month	0.006	0.126	-0.047	0.106	0.049	0.106	0.319*	0.125	0.251*	0.113
Number of behavioral reminders	0 per week (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	1 per week	-0.005	0.130	-0.007	0.123	-0.015	0.107	0.260*	0.121	0.136	0.111
	3 per week	-0.071	0.118	0.231*	0.104	0.036	0.098	0.405**	0.109	0.065	0.100
	1 per day	0.013	0.118	0.129	0.101	0.068	0.097	0.358**	0.109	0.230*	0.103

Table 7.4: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Total expenditure on nutrition		-0.044**	0.003	-0.027**	0.002	-0.015**	0.001	-0.028**	0.002	-0.011**	0.001
Use of time	5 minutes more per day (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	15 minutes more per day	-0.164	0.115	0.081	0.103	0.065	0.094	0.126	0.106	0.038	0.101
	30 minutes more per day	-0.306*	0.118	-0.113	0.102	-0.041	0.095	-0.076	0.108	0.002	0.100
	60 minutes more per day	-0.474**	0.133	-0.286**	0.101	-0.212*	0.098	-0.217	0.113	-0.041	0.106
Expected outcomes	Longer life expectancy and weight loss of up to 0 kilograms after 4 months (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	Longer life expectancy and weight loss of up to 2 kilograms after 4 months	0.444**	0.130	0.341**	0.108	0.471**	0.109	0.253*	0.122	0.418**	0.114
	Longer life expectancy and weight loss of up to 4 kilograms after 4 months	0.456**	0.123	0.256*	0.108	0.653**	0.104	0.416**	0.112	0.735**	0.106
	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	0.564**	0.130	0.428**	0.111	0.888**	0.122	0.663**	0.128	0.927**	0.114

Table 7.4: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
SD											
Constant (opt-out)		2.943**	0.196			2.375**	0.154	2.693**	0.185	2.381**	0.145
Meals provided	Personalized dinner	0.000	x	0.000	x	0.000	x	0.000	x		
	Personalized lunch and dinner	-0.098	0.279	0.370*	0.188	0.130	0.226	0.475*	0.228		
	Personalized breakfast and dinner	0.650**	0.225	0.967**	0.164	0.622**	0.164	-0.679**	0.188		
	Personalized breakfast, lunch, and dinner	-0.088	0.202	-0.066	0.138	0.113	0.222	0.564**	0.202		
Number of dietitian appointments	0 per month (ref)	0.000	x	0.000	x	0.000	x	0.000	x	0.000	x
	1 per month	1.412**	0.197	1.355**	0.162	0.923**	0.151	0.838**	0.173	0.686**	0.175
	2 per month	-0.009	0.264	-0.307	0.216	0.330	0.170	-0.139	0.205	-0.105	0.257
	3 per month	0.434	0.364	-0.250	0.242	0.429	0.222	0.857**	0.184	-0.512*	0.215
Number of behavioral reminders	0 per week (ref)			0.000	x			0.000	x		
	1 per week			0.871**	0.168			0.729**	0.184		
	3 per week			-0.196	0.318			-0.043	0.196		
	1 per day			-0.187	0.275			0.137	0.232		

Table 7.4: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Total expenditure on nutrition		0.037**	0.003	0.031**	0.002	0.019**	0.001	0.028**	0.002	-0.009**	0.001
Use of time	5 minutes more per day (ref)	0.000	x					0.000	x	0.000	x
	15 minutes more per day	-0.128	0.184					-0.006	0.169	-0.027	0.180
	30 minutes more per day	-0.105	0.300					0.494*	0.217	0.013	0.251
	60 minutes more per day	0.862**	0.213					0.639**	0.229	0.585**	0.216

Table 7.4: Continued.

Attributes	Level	The Netherlands		UK		US		Spain		Poland	
		Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.	Coefficient	Std.err.
Expected outcomes	Longer life expectancy and weight loss of up to 0 kilograms after 4 months (ref)	0.000	x			0.000	x	0.000	x	0.000	x
	Longer life expectancy and weight loss of up to 2 kilograms after 4 months	0.618**	0.220			-0.106	0.440	-0.582**	0.148	-0.355	0.231
	Longer life expectancy and weight loss of up to 4 kilograms after 4 months	-0.358	0.290			-0.239	0.228	0.119	0.182	-0.052	0.232
	Longer life expectancy and weight loss of up to 6 kilograms after 4 months	0.300	0.303			0.894**	0.153	0.559*	0.237	-0.202	0.515

* Significant at P < 0.05. ** Significant at P < 0.01

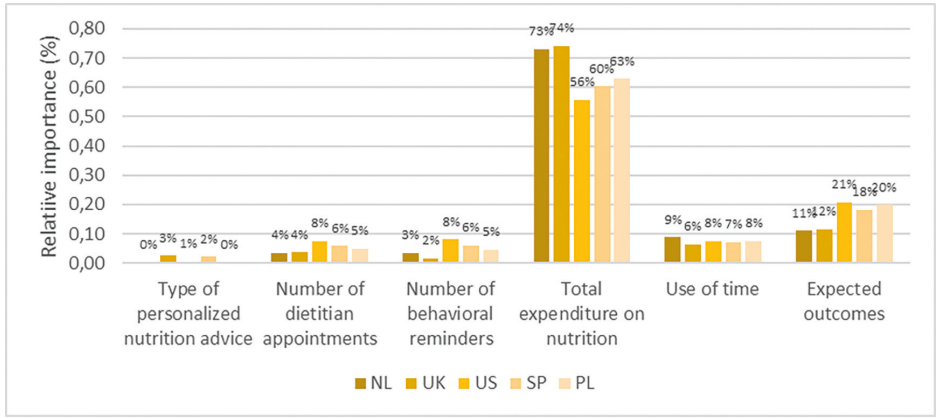


Figure 7.3: Relative importance (in %) of attributes in 'PN advice' based on the panel MIXL, stratified by country. *Note: NL, Netherlands; UK, United Kingdom; US, United States; SP, Spain; PL, Poland.*

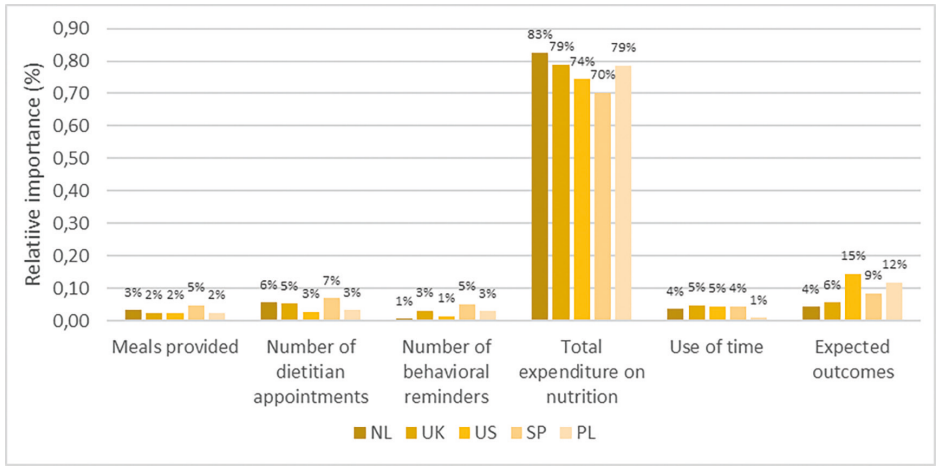


Figure 7.4: Relative importance (in %) of attributes in 'Personalized meals' based on the panel MIXL, stratified by country. *Note: NL, Netherlands; UK, United Kingdom; US, United States; SP, Spain; PL, Poland.*

Willingness to pay

Final WTP estimates are shown in Table 7.5. For the 'PN advice' intervention, the WTP increases as the expected weight loss resulting from 'PN advice' also increases. Overall, highest WTP estimates were found for six kilograms of weight loss. Respondents from Poland were willing to spend an extra 16.63 euros per week during the intervention period (four months) for an anticipated weight loss of six kilograms after those four months compared to zero kilograms. The uncertainty around this estimate (Interquartile range (IQR)) is worth mentioning. More specifically, the highest WTP within the IQR that people want to spend extra per week for PN

advice is 37.39 euros. Respondents in the UK seemed to be willing to pay least for 'PN advice', which was 1.82 euros per week for two kilograms of anticipated weight loss after four months. Moreover, the general population with a current expenditure on nutrition that was labeled as 'high', were willing to pay more for 'PN advice' than respondents who had an expenditure on nutrition labeled as 'low'. However, opposite results were found for two kilograms of weight loss and six kilograms of weight loss in the US. It is however worth mentioning, that there was also uncertainty found around these WTP estimates. More details about the WTP divided by total expenditure can be found in Appendix 7.5.

For the 'personalized meals' intervention, the WTP increases as well if the expected weight loss resulting from 'personalized meals' is increasing. The general population were willing to pay most for 'personalized meals' in Poland, where they would be willing to pay an extra 25.78 euros per week during the intervention period for six kilograms of anticipated weight loss after four months compared to zero kilograms. Additionally, higher WTP estimates were found for 'personalized meals' when respondents' current expenditure on nutrition was labeled as 'high', compared to when respondents' current expenditure on nutrition was labeled as 'low'. The smallest difference was found in the UK for four kilograms of weight loss, where the WTP was 0.93 euros higher in the 'high' labeled group compared to the 'low' labeled group. The largest difference was found in Poland for six kilograms of weight loss, where the WTP was 7.50 euros higher in the 'high' labeled group compared to the 'low' labeled group.

Table 7.5: Willingness to pay (WTP) for losing weight, stratified by country.[a]

'PN advice'														
	The Netherlands			**UK**			**US**			**Spain**			**Poland**		
	Median	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*
2 kg loss	5.97	3.89	12.05	1.82	1.20	5.51	4.89	-3.12	14.32	8.26	3.91	20.38	10.19	6.26	21.20
4 kg loss	9.06	6.79	18.15	6.73	4.65	20.73	11.61	2.88	28.74	12.60	7.38	28.26	16.96	11.73	31.57
6 kg loss	9.21	3.89	8.27	9.20	-0.54	24.84	14.61	-6.33	42.12	16.43	3.02	38.89	16.63	10.00	37.39
'Personalized meals'															
	The Netherlands			**UK**			**US**			**Spain**			**Poland**		
	Median	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*	*Median*	*IQR (25)*	*IQR (75)*
2 kg loss	6.45	1.49	14.63	8.24	4.90	24.66	12.47	7.74	32.91	7.15	-2.74	23.39	11.38	7.99	23.31
4 kg loss	7.03	4.09	16.16	6.18	3.67	18.49	16.28	10.30	46.41	13.12	7.33	31.88	20.44	14.33	42.54
6 kg loss	8.61	5.61	18.48	10.34	6.15	30.96	20.95	-2.35	59.45	18.41	6.67	48.65	25.78	18.33	53.19

Note: [a] Medians, including the IQR were reported, since parameters were not normally distributed. The WTP, compared with the reference level of 0 kg, is given in Euros. IQR, interquartile range; kg, kilograms; PN, personalized nutrition; UK, United Kingdom; US, United States.

Potential participation rate

The results in Table 7.6 show that the least preferred PN advice also had the lowest predicted participation rate, ranging from 19% in the Netherlands to 34% in Spain. This least preferred PN advice was constructed by finding the attribute levels that were most often least preferred in the different countries. The participation rate for two PREVENTOMICS interventions related to the PN advice were approximately the same, since only one attribute level differed (i.e., type of personalized nutrition advice). These participation rates ranged from 29% in the Netherlands to 49% in Spain, with slightly higher uptake for PN advice on recipes instead of products. The most preferred PN advice was associated with an estimated potential participation ranging from 70% in the UK and US to 81% in Spain.

The predicted uptake for the 'personalized meals' intervention is shown in Table 7.7. This intervention is somehow comparable with the PREVENTOMICS intervention that studied personalized meals, and therefore the predicted uptake for this scenario was calculated. The 'real' costs of this intervention are uncertain but could be estimated to be either the third level of the cost attribute (163 euros) or the fourth level (244 euros), which is why we showed the uptake of both scenarios. For a cost level of 163 euros, this participation rate ranged from 31% in the Netherlands and Poland to 48% in Spain. This was slightly lower for a cost level of 244 euros. The least preferred intervention, constructed in the same way as described by 'PN advice', resulted in an uptake ranging from 18% in the Netherlands to 34% in Spain. Moreover, the uptake for the most preferred intervention ranged from 73% in the UK to 87% in Spain.

Table 7.6: Expected participation rates (predicted uptake) for different PN intervention scenarios, based on the attribute estimates of the MIXL model for 'PN advice'.

	Predicted uptake mean (%)					Explanation
	The Netherlands	The UK	The US	Spain	Poland	
Least preferred	19%	29%	32%	34%	25%	PN with advice on products, 3 dietitian sessions per month, 0 reminders per week, highest cost level, 60 minutes of extra time and 0 kg of weight loss.
PN advice on recipes: PREVENTOMICS intervention~	29%	37%	41%	49%	39%	PN with advice on recipes, 1 dietitian session per month, 1 reminder per week, level 3 on costs, 60 minutes of extra time and 2 kg of weight loss.
PN advice on products: PREVENTOMICS intervention⁺	29%	35%	41%	48%	37%	Same as PREVENTOMICS intervention with advice on recipes, but then with advice on specific food products.
Preferred intervention	73%	70%	70%	81%	75%	PN with advice on recipes, 1 dietitian session per month, 1 reminder per day, level 1 on costs (0 euros), 5 minutes of extra time and 6 kg of weight loss.

Note: ~PREVENTOMICS intervention carried out in Poland and the UK. ⁺PREVENTOMICS intervention carried out in Spain. PN, personalized nutrition; UK, United Kingdom; US, United States.

Table 7.7: Expected participation rates (predicted uptake) for different PN intervention scenarios, based on the attribute estimates of the MIXL model for 'Personalized meals'.

	Predicted uptake mean (%)					Explanation
	The Netherlands	The UK	The US	Spain	Poland	
Least preferred	18%	27%	30%	34%	21%	Personalized meals with all 3 meals delivered, 1 dietitian session per month, 1 reminder per week, highest cost level, 60 minutes extra time and 0 kg of weight loss.
Personalized meals with a cost level of 163 euros: PREVENTOMICS intervention~	31%	38%	42%	48%	32%	Personalized meals with lunch and dinner delivered, 0 dietitian sessions per month, 1 reminder per week, level 3 on costs, 5 minutes extra time and 2 kg of weight loss.
Personalized meals with a cost level of 244 euros: PREVENTOMICS intervention~	26%	33%	36%	41%	25%	Same as PREVENTOMICS intervention with a cost level of 163 euros, but then with a cost level of 244 euros.
Preferred intervention	76%	73%	78%	87%	80%	Personalized meals with lunch and dinner delivered, 1 dietitian session per month, 3 reminders per week, level 1 on costs (0 euros), 15 minutes extra time and 6 kg of weight loss.

Note: ~PREVENTOMICS intervention carried out in Denmark. Kg, kilograms; PN, personalized nutrition; UK, United Kingdom; US, United States.

Attribute level estimates differences and scale parameter

MNL models of all five countries were used to perform the Swait and Louviere test. Based on the results of the chi-square tests, we can reject the hypothesis of equal attribute level estimates ($p < 0.05$). In other words, despite correcting for possible scale differences, the differences in attribute level estimates between the Netherlands and the UK, US, Spain, or Poland were statistically significant. Thus, the differences that we found in the datasets are because of significant differences in preferences (and likely also scale differences) in the countries.

DISCUSSION

This study aimed to gain insight into the preferences for PN interventions as well as to show the WTP for PN interventions and to calculate the participation rates for hypothetical PN interventions in the general population in Europe and US. People's preferences for specific interventions are important for informing PN development, implementation, and reimbursement decisions. From the results, we can conclude that for the two PN interventions that were studied (i.e., PN advice and personalized meals), a low 'total expenditure on nutrition' was the most crucial factor for respondents in all countries when deciding to choose a PN intervention. This was expected, as PN interventions are generally not reimbursed in these European countries and the US (321,356,380,418). Moreover, we found that respondents are willing to use PN interventions; the predicted uptake for the most preferred 'PN advice' intervention and for the most preferred 'personalized meals' intervention was different across countries (all uptake higher than 70%) and was highest in Spain, with an uptake of 81% and 87% respectively. The least preferred intervention also showed different uptake across countries (e.g., 34% in Spain for 'personalized meals' compared to 18% in the Netherlands). This indicates that in some countries such as Spain, the a priori uptake is already higher compared to, for example, the Netherlands. The interest in PN interventions might be higher in countries such as Spain. Notably, adjusting the levels of the interventions resulted in an increased participation rate in the Netherlands (i.e., 76% for 'personalized meals'), aligning it more closely with the participation rate in the US (i.e., 78%). This suggests that the participation rate in the Netherlands might be more influenced by the specific content of the intervention than in other countries.

The WTP for the interventions varied per country, per intervention and per change in anticipated kilograms of weight loss. Overall, the highest WTP for both 'PN advice' and 'personalized meals' during the intervention period was found for six kilograms of anticipated weight loss after four months. For example, the highest WTP that people want to spend during the intervention period for 'personalized meals' was an extra 25.78 euros per week for six kilograms of anticipated weight loss after four months, compared to zero kilograms.

To our knowledge, this is the first study that investigated people's preferences for two specific types of high level PN interventions in Europe and US. However, preference research

has been conducted on nutrition interventions (personalized or not) with slightly other focusses or methods than used in this study. The relatively high WTP reported for six kilograms of weight loss is in line with previous research on patient preferences for diabetes management (70,408). Moreover, the sensitivity of the respondents to an increase in costs and the limited value that respondents attach to behavior change is also in line with previous research by Ryan et al. (402) who investigated the preferences of the general population in the UK for lifestyle interventions.

A study by Perez-Troncoso et al. (389) also showed that respondents were willing to pay for PN interventions. They used latent class logit models to reveal four classes of respondents and showed one class with respondents that would be likely to pay for a high level of PN service. In the other classes people were less or not at all inclined to pay for PN interventions. Similar to our study, these results showed that there is a market for PN, but that there is heterogeneity in the preferences of people regarding PN and their WTP. Both 'total expenditure' and 'expected outcomes' were set at random in most countries with the panel MIXL models in our study, indicating heterogeneity in the value attached to these attributes and thereby also in the WTP for PN to lose weight. This argument is strengthened by the result that respondents with a higher current expenditure on nutrition are generally willing to pay more compared to people with a lower current expenditure.

Future research should explore the heterogeneity found in this study and to investigate what groups are most willing to pay for and to use PN interventions (e.g., latent class modeling) (402,419). Earlier research showed for example that a group of people who had a high prevalence of NCDs were more interested in a high level of PN and were willing to pay more (389). Moreover, it could be expected that respondents with a higher income, and thus more ability to pay, are more willing to pay for PN interventions (420). It would also be interesting to investigate, for example, how goals (both health related or non-health related) of individuals influence preferences for PN interventions, since a study by Benning et al. (421) showed that this could play an important role in individuals' health related decisions. Additionally, people's eating context could have a potential role on people's intention to use PN (422). For example, eating outside the home could be seen as a potential barrier to keep using PN interventions, and it would therefore be interesting to see if and how this explains heterogeneity in preferences of people regarding PN interventions. Lastly, by declaring heterogeneity in DCEs, it would be interesting to pay attention to the social and mental support of people, since this might influence their preferences (423).

Comparisons of the relative importance of the different attributes showed the importance of the cost components for the general population, whereas all other attributes were less important. The participation rates that we calculated for two scenarios for 'personalized meals' of the PREVENTOMICS intervention, in which we only varied the cost level, showed the sensitivity to costs as well. These rates showed that when costs were increased to the next cost level, participation rates decreased by 5-7% across countries. This indicates that

respondents were quite sensitive to an increase in costs. These results complement earlier studies (70,402,424,425) and suggest that developers of PN interventions should focus on PN interventions with low costs, try to obtain public subsidies for some or all of the costs, or use financial incentives to increase the uptake of PN interventions that lead to greater weight loss, and thereby prevent diet-related diseases and increase life expectancy. Public subsidies of some of the costs would decrease the amount that individuals need to pay out-of-pocket to participate in a PN intervention. Payers might be interested in partly subsidizing (i.e., co-financing) PN interventions for specific subpopulations. Future research could study which subpopulations should receive financial subsidies (e.g., people with diabetes and a low income).

Another possible way to increase uptake of PN interventions is by using financial incentives. A study by Molema et al. (426) showed that a preferred type of incentive is to reward participants after completing a lifestyle program with a cash reward of 100 euros, if the participant attended at least 75% of the scheduled meetings. Something comparable could be done by PN interventions to increase uptake. Another way to increase uptake and thereby increase (and maintain) weight loss is a 'commitment lottery' where winners are drawn from all participants but can only claim their prize (100 euros) if they also attained their goals (427). Since these lotteries are known to be effective in increasing physical activity for up to 52 weeks (427), this commitment lottery could increase the uptake of PN interventions and thereby increase their effectiveness.

Strengths and limitations

This study has several strengths. First, we followed good research practices, where we used qualitative methods, such as focus groups for attribute and level development and think-aloud sessions for testing the questionnaire (64,395). The DCEs validated the results of the focus groups and those from other studies, where the price was also found to be very important, providing face/ theoretical validity of our study outcomes. Second, the inclusion of five different countries in this DCE, comprising European countries from the northern, eastern, southern, and western Europe and the US, with data of at least 500 respondents per country, gives a good overview of the preferences in different countries and might be a starting point to investigate preferences in more countries.

This study also has some limitations. First, due to practical reasons, focus groups and think aloud sessions were only done in the Netherlands. However, since no large differences in preference structures between countries were found, it can be concluded that this had no impact on the validity of the outcomes of our DCEs. Second, we used online panels to recruit the respondents for our study. In this way, only respondents with access to the internet were recruited, which might potentially lead to selection bias. However, earlier research has shown that there is no indication that online surveys yield inferior results compared with paper-based surveys (428).

Third, we did not randomize the order in which our two DCEs were shown to the respondents; 'PN advice' was always shown first. Additionally, before the choice tasks of 'personalized meals' were shown to the respondent, we asked respondents for their ability to get by in terms of money. This could have changed the way respondents thought about their WTP for a PN intervention. However, we expected that people's WTP for 'personalized meals' was higher than for 'PN advice' and our results confirm this. Moreover, as expected, respondents with a higher current expenditure on nutrition had a higher WTP compared to people with a lower expenditure, indicating theoretical validity and reliability of our results.

Fourth, we found some differences between our quantitative study results (i.e., the DCE) and the qualitative study (i.e., focus groups). In our quantitative study, respondents attached much more value to costs than other attributes, whereas respondents in our qualitative study stated that other attributes were important as well. This might indicate that respondents in our qualitative part gave socially desirable answers. Moreover, research has shown that framing (i.e., how information is presented) of different attributes can influence the WTP (429). 'Total expenditure on nutrition' was in our WTP calculation defined as the proxy for costs, which included two components of expenditure per week. Framing these costs in costs per week instead of per day/month/year, might have influenced the WTP outcomes. Future research should test this hypothesis.

Lastly, an important shortcoming of DCEs in general is that it is rarely possible to include all possible attributes and levels, meaning that results are contingent upon having selected only the most important attributes of choice. Previous studies have however shown that well designed DCE studies predict up to 91% of individual choices in real life (430).

CONCLUSION

The general population seems to be willing to pay for PN interventions to lose weight and thereby to prevent NCDs. However, their WTP might not cover the actual costs for PN, which raises questions about who would pay for PN interventions that are worth implementing. To increase uptake for PN interventions, this study suggests several options: (partly) subsidizing costs, financial incentives and commitment lotteries. Moreover, it is important for developers of PN interventions to keep the costs as low as possible since people are most sensitive to the costs; whether this is because of the WTP or the ability to pay can be debated. More research is needed to explain the heterogeneity in preferences within the countries (e.g., latent class modeling), since our models showed preference heterogeneity between, but also within, the different countries, and this might result in specific recommendations for specific groups within countries.

APPENDICES

Appendix 7.1: Details about the focus group studies

1. Aim

The primary aim of these focus groups was to explore the preferences of the general population regarding characteristics of personalized nutrition (PN) interventions. Results were used as input for designing discrete choice experiments (DCEs).

2. Methods

The focus group studies were conducted following the guideline of Krueger (403). In summary, this guideline provides information on what the ideal characteristics of the focus group studies would be, skills for the moderator and recorder, an outline of the focus groups, information relevant for the beginning of the focus group discussion, information on what powerful questions are, information for taking notes, and information for analyzing the focus group studies. The last mentioned includes recommendations for different moments in time, which starts already with recommendations for analyzing when still in the group (e.g., listen for vague or cryptic comments and probe for understanding) and ends with the final reporting of the results (e.g., consideration of narrative style).

3. Results and conclusion

We did three separate focus group sessions with six participants in each session. The discussions that arose during these sessions helped us to gain important insights into the preferences of people regarding different characteristics of PN interventions. It was found that most participants showed a general willingness to use a certain PN intervention. However, it was found that several characteristics of PN interventions influence their likelihood to use a certain intervention:

1. Price

As expected, price seemed particularly important for people. In other words, their willingness to pay for an intervention seemed important. We also found that the maximum willingness to pay was lower for app-assisted grocery shopping (30 euros) than for home delivery of meals (300 euros).

2. Intervention type

Participants were asked what kind of PN interventions they could think of. This varied widely from home meal delivery to different mobile apps. The participants with a younger age, preferred the meal delivery while older participants more often preferred app-assisted interventions.

3. Extra time

Participants preferred not to spend any extra time using the intervention; if they needed to spend extra time, they did not want this to be any longer than 15 minutes, including everything related to the intervention.

4. User-friendliness

This especially related to the app-assisted interventions, where participants think it is important to have an intervention that is easy to use.

5. Privacy

Participants were somewhat skeptical about privacy risks from the personalization of interventions. What do researchers want to do with this information? They might be more willing to use the intervention if it is provided and supported by the government, since they believe privacy-related issues might be better managed in that way.

6. Personal goal

Participants also believe that the willingness to use an intervention depends on people's personal goals. Some participants from the focus groups did not have a personal goal related to health and were therefore less willing to use an intervention. In contrast, others did have a personal goal such as feeling more energetic or weight loss and were therefore willing to use an intervention.

7. Taste

Participants stated that taste is very important. They believe that the quality of the taste will improve adherence to the intervention's regimen.

8. Evidence of effectiveness

Moreover, participants want to have some evidence of effectiveness before they use the intervention. Participants were less willing to use an intervention if there is not any evidence for effectiveness or if the evidence is unclear.

All of these characteristics might influence the likelihood to use a certain intervention. However, there was much heterogeneity in the preferences of the people who participated in these focus group studies. In order to see the relative relevance of all these characteristics and to quantify the heterogeneity in people, a DCE is needed.

Appendix 7.2: Equations for the main effect models that were used

Equations 1 ('PN advice') and 2 ('personalized meals') show the main effects models that were used to estimate the utility.

$$U = V + \varepsilon = \beta 0 + \beta 1 * \text{Type of personalized nutrition advice}_{\text{Advice food products via app}} + \beta 2 * \text{Number of dietitian appointments}_{\text{1 per month}} + \beta 3 * \text{Number of dietitian appointments}_{\text{2 per month}} + \beta 4 * \text{Number of dietitian appointments}_{\text{3 per month}} + \beta 5 * \text{Number of behavioral reminders}_{\text{1 per week}} + \beta 6 * \text{Number of behavioral reminders}_{\text{3 per week}} + \beta 7 * \text{Number of behavioral reminders}_{\text{1 per day}} + \beta 8 * \text{Total expenditure on nutrition} + \beta 9 * \text{Use of time}_{\text{15 minutes more per day}} + \beta 10 * \text{Use of time}_{\text{30 minutes more per day}} + \beta 11 * \text{Use of time}_{\text{60 minutes more per day}} + \beta 12 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 2 kilograms after 4 months}} + \beta 13 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 4 kilograms after 4 months}} + \beta 14 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 6 kilograms after 4 months}} + \varepsilon \quad \textbf{(1)}$$

$$U = V + \varepsilon = \beta 0 + \beta 1 * \text{Meals provided}_{\text{personalized lunch and dinner}} + \beta 2 * \text{Meals provided}_{\text{personalized breakfast and dinner}} + \beta 3 * \text{Meals provided}_{\text{personalized breakfast, lunch, and dinner}} + \beta 4 * \text{Number of dietitian appointments}_{\text{1 per month}} + \beta 5 * \text{Number of dietitian appointments}_{\text{2 per month}} + \beta 6 * \text{Number of dietitian appointments}_{\text{3 per month}} + \beta 7 * \text{Number of behavioral reminders}_{\text{1 per week}} + \beta 8 * \text{Number of behavioral reminders}_{\text{3 per week}} + \beta 9 * \text{Number of behavioral reminders}_{\text{1 per day}} + \beta 10 * \text{Total expenditure on nutrition} + \beta 11 * \text{Use of time}_{\text{15 minutes more per day}} + \beta 12 * \text{Use of time}_{\text{30 minutes more per day}} + \beta 13 * \text{Use of time}_{\text{60 minutes more per day}} + \beta 14 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 2 kilograms after 4 months}} + \beta 15 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 4 kilograms after 4 months}} + \beta 16 * \text{Expected outcomes}_{\text{Longer life expectancy and weight loss of up to 6 kilograms after 4 months}} + \varepsilon \quad \textbf{(2)}$$

V describes here the measurable utility of a specific PN intervention based on the attributes that were included in the DCE. The constant β0 was included as an alternative specific constant term for the alternative that was presented last (i.e., the opt-out). β1- β16 are the utility coefficients estimates for the attributes measured, that indicate the relative importance of each attribute level. The opt-out was modeled to have zero utility.

Appendix 7.3: Respondents' characteristics

Table 7.3.1: Respondents' characteristics.[a]

	The Netherlands (n=513)	UK (n=525)	US (n=516)	Spain (n=501)	Poland (n=501)	P-value
Age, median (IQR)	48 (36-56)	43 (34-53)	47 (35-57)	42 (33-52)	39 (30-51)	<0.001[+]
Gender, n (%)						0.209[+]
Male	222 (43.3)	242 (46.1)	226 (43.8)	246 (49.1)	243 (48.5)	
Female	290 (56.5)	279 (53.1)	288 (55.8)	255 (50.9)	258 (51.5)	
Prefer not to say	1 (0.2)	1 (0.2)	1 (0.19)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	3 (0.6)	1 (0.19)	0 (0.0)	0 (0.0)	
Weight, median (IQR)	77 (66-88)	75 (63-90)	75 (60-90)	70 (60-80)	74 (63-85)	<0.001[~]
BMI (kg/m2), median (IQR)	24.8 (22.4-27.9)	24.9 (21.6-29.6)	25.4 (21.4-31.4)	24.2 (21.6-26.6)	24.8 (21.6-27.6)	<0.001[~]
Weight category, n (%)[$]						<0.001[~]
Underweight	24 (4.7)	55 (10.5)	71 (13.8)	31 (6.2)	24 (4.8)	
Healthy weight	241 (47.0)	211 (40.2)	176 (34.1)	273 (54.5)	238 (47.5)	
Overweight	170 (33.1)	130 (24.8)	113 (21.9)	136 (27.2)	165 (32.9)	
Obese	78 (15.2)	129 (24.6)	156 (30.2)	61 (12.2)	74 (14.8)	
Educational level*						<0.001[+]
Low	84 (16.4)	59 (11.2)	17 (3.3)	44 (8.8)	32 (6.4)	
Medium	215 (41.9)	81 (34.5)	195 (37.8)	122 (24.4)	207 (41.3)	
High	212 (41.3)	279 (53.1)	302 (58.5)	321 (64.1)	250 (49.9)	
Other	2 (0.4)	6 (1.1)	2 (0.4)	14 (2.8)	12 (2.4)	

Table 7.3.1: Continued.

	The Netherlands (n=513)	UK (n=525)	US (n=516)	Spain (n=501)	Poland (n=501)	P-value
Household size, n (%)						<0.001⁺
1	137 (26.7)	131 (25.0)	112 (21.7)	59 (11.8)	42 (8.4)	
2	197 (38.4)	166 (31.6)	171 (33.1)	129 (25.8)	108 (21.6)	
3	84 (16.4)	104 (19.8)	101 (19.6)	157 (31.3)	161 (32.1)	
4	72 (14.0)	92 (17.5)	96 (18.6)	120 (24.0)	126 (25.2)	
5	17 (3.3)	22 (4.2)	26 (5.0)	29 (5.8)	41 (8.2)	
6	1 (0.2)	6 (1.1)	5 (1.0)	5 (1.0)	14 (2.8)	
7 or more	5 (1.0)	4 (0.8)	5 (1.0)	2 (0.4)	9 (1.8)	
Ability for someone to get by in terms of money, n (%)						<0.001⁺
Lot of effort	51 (9.9)	121 (23.1)	109 (21.1)	81 (16.2)	43 (8.6)	
Some effort	184 (35.8)	214 (40.8)	187 (36.2)	283 (56.5)	267 (53.3)	
Pretty easy	179 (34.9)	136 (25.9)	146 (28.3)	52 (10.4)	164 (32.7)	
Easy	99 (19.3)	54 (10.3)	74 (14.3)	85 (17.0)	27 (5.4)	
General health						<0.001⁺
Very good	68 (13.3)	98 (18.7)	143 (27.7)	65 (13.0)	59 (11.8)	
Good	303 (59.1)	240 (45.7)	237 (45.9)	297 (59.3)	250 (49.9)	
Moderate	123 (23.4)	154 (29.3)	114 (22.1)	122 (24.4)	172 (34.3)	
Bad	17 (3.3)	23 (4.4)	21 (4.1)	14 (2.8)	16 (3.2)	
Very bad	2 (0.4)	10 (1.9)	1 (0.2)	3 (0.6)	4 (0.8)	

Table 7.3.1: Continued.

	The Netherlands (n=513)	UK (n=525)	US (n=516)	Spain (n=501)	Poland (n=501)	P-value
Chronic disease yes, n (%)[$]	170 (33.1)	128 (24.4)	160 (31.0)	166 (33.1)	177 (35.3)	0.002⁺
Diabetes I, n (%)	20 (11.8)	13 (10.2)	20 (12.5)	10 (6.0)	23 (13.0)	0.236⁺
Diabetes II, n (%)	33 (19.4)	37 (28.9)	54 (33.8)	25 (15.1)	30 (17.0)	0.000⁺
Heart disease, n (%)	22 (12.9)	10 (7.8)	17 (10.6)	12 (7.2)	26 (14.7)	0.139⁺
Stroke, n (%)	14 (8.2)	7 (5.5)	7 (4.4)	3 (1.8)	0 (0.0)	0.001⁺
Crohn's disease, n (%)	14 (8.2)	13 (10.2)	12 (7.5)	9 (5.4)	2 (1.1)	0.011⁺
Kidney disease, n (%)	10 (5.9)	4 (3.1)	6 (3.8)	2 (1.2)	11 (6.2)	0.123⁺
Metabolic disease, n (%)	7 (4.1)	2 (1.6)	12 (7.5)	11 (6.6)	12 (6.8)	0.156⁺
Mental illness, n (%)	27 (15.9)	31 (24.2)	29 (18.1)	25 (15.1)	9 (5.1)	<0.001⁺
Cancer, n (%)	7 (4.1)	5 (3.9)	9 (5.6)	3 (1.8)	6 (2.4)	0.488⁺
Other, n (%)	83 (48.8)	51 (39.8)	64 (40.0)	88 (53.0)	93 (52.5)	0.032⁺
Healthy diet, n (%)[#]	206 (40.2)	152 (29.0)	119 (23.1)	142 (28.3)	112 (22.4)	<0.001⁺
Physically active, n (%)[^]	245 (47.8)	190 (36.2)	186 (36.1)	158 (31.5)	132 (26.4)	<0.001⁺
Currently using a nutrition intervention, n (%)	84 (16.4)	173 (33.0)	181 (35.1)	165 (32.9)	179 (35.7)	<0.001⁺

Note: [a] frequencies (n), including percentages (%), or the median with the IQR where shown. Differences between countries were tabulated (p-value) and calculated via the Kruskal Wallis (~) or the chi-squared test (+). Education was divided into 3 categories (*): Low: primary education plus the first three years of senior general secondary education and pre-university secondary education, various pathways of prevocational secondary education. Medium: upper secondary education, (basic) vocational training, middle management, and specialist education. High: associate degree programs, higher education bachelor programs, 4-year education at universities of applied sciences, master's degree, and doctoral degree. People were categorized as underweight if their BMI <18.5 kg/m², healthy weight if BMI 18.5-24.9 kg/m², overweight if BMI 25-29.9 kg/m² and obese if BMI =>30 kg/m² ($). People were considered to eat a healthy diet when they reported eating balanced meals a minimum of 6 days per week (varied, not too much, not too fat and vegetables and fruits) (#) People were considered inactive if they performed no more than 30 minutes of activity on less than 5 days a week (^). Respondents could have more than one disease at the same time ($).

Appendix 7.4: Testing for dominant decision-making results

Table 7.4.1: Proportion of respondents that dominate in their choice for their current eating style (i.e., opt-out) and for the PN intervention with the lowest cost level.

	The Netherlands		Spain		Poland		The UK		The US	
	Number of people	Percentage of total number (n=516)	Number of people	Percentage of total number (n=501)	Number of people	Percentage of total number (n=501)	Number of people	Percentage of total number (n=513)	Number of people	Percentage of total number (n=525)
'PN advice'										
Respondents choose always opt-out (current eating style)	68	13.3	30	6.0	55	11.0	51	9.7	50	9.7
Respondents choose always PN with the lowest costs level	4	0.8	13	2.6	5	1.0	5	1.0	3	0.6
'Personalized meals'										
Respondents choose always opt-out (current eating style)	47	9.2	24	4.8	36	7.2	43	8.2	37	7.2
Respondents choose always PN with the lowest costs level	10	1.9	11	2.2	8	1.6	5	1.0	7	1.4

Appendix 7.5: Willingness to pay divided by total current expenditure

Table 7.5.1: Willingness to pay for losing weight, divided by low or high amount of current expenditure on nutrition for 'PN advice'.[a]

		The Netherlands			The UK		
	Expenditure on nutrition	Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)
2 kg loss	Low	5.66	3.97	10.18	1.74	1.20	6.14
	High	6.11	3.76	13.70	1.97	1.21	5.00
4 kg loss	Low	8.62	6.80	15.39	6.29	4.57	21.42
	High	9.40	6.67	21.04	7.25	4.71	19.58
6 kg loss	Low	8.93	4.39	15.52	8.29	-1.88	22.74
	High	9.25	3.16	19.40	9.35	1.17	27.19

Table 7.5.1: Continued.

The US			Spain			Poland		
Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)
5.06	-1.82	14.55	6.99	3.79	16.73	9.58	6.24	14.73
4.77	-6.38	14.25	11.01	4.88	22.97	11.50	6.39	28.27
11.59	4.43	30.44	11.82	7.53	24.55	16.17	11.30	24.41
11.73	-9.09	24.94	14.94	7.15	30.59	19.76	12.20	62.88
16.29	-4.38	40.02	15.48	2.32	35.81	15.71	10.43	29.12
13.16	-11.71	47.78	17.33	4.66	40.22	18.95	9.49	60.97

Note: [a] Medians, including the IQR were reported, since parameters were not normally distributed. The WTP, compared with the reference level of 0 kg, is given in Euros. IQR, interquartile range; kg, kilograms; PN, personalized nutrition; UK, United Kingdom; US, United States

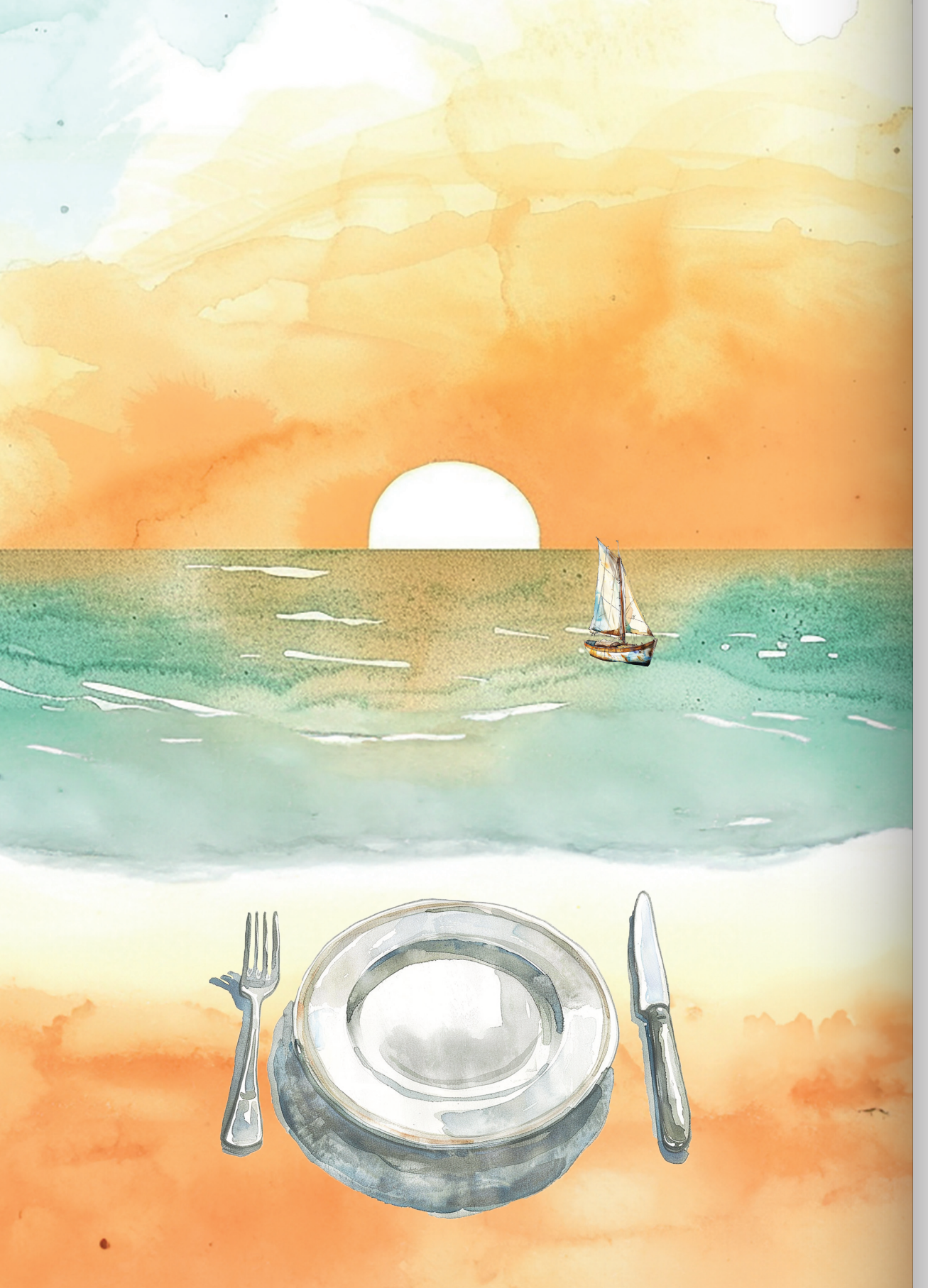
Table 7.5.2: Willingness to pay for losing weight, divided by low or high amount of current expenditure on nutrition for 'Personalized meals'.[a]

		The Netherlands			The UK		
	Expenditure on nutrition	Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)
2 kg loss	Low	5.35	1.27	10.34	7.43	4.73	21.48
	High	8.23	1.93	23.12	8.67	5.09	25.78
4 kg loss	Low	6.59	3.82	10.45	5.56	3.55	16.10
	High	8.42	4.29	23.76	6.50	3.81	19.33
6 kg loss	Low	7.40	5.30	13.03	9.32	5.94	26.95
	High	9.71	5.92	26.50	10.88	6.39	32.35

Table 7.5.2: Continued.

The US			Spain			Poland		
Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)	Median	IQR (25)	IQR(75)
10.94	8.01	31.43	6.28	-3.07	19.69	10.59	7.97	18.08
13.53	6.30	34.07	8.33	-2.41	29.30	12.91	8.18	32.89
15.42	10.55	41.46	11.59	7.15	31.83	18.83	14.15	31.91
16.94	7.51	47.98	14.80	7.39	32.01	23.77	15.72	61.12
19.80	1.01	53.45	16.25	5.38	42.72	23.01	17.87	39.89
22.42	-16.54	64.73	22.64	7.75	55.31	30.50	19.64	77.46

Note: [a] Medians, including the IQR were reported, since parameters were not normally distributed. The WTP, compared with the reference level of 0 kg, is given in Euros. IQR, interquartile range; kg, kilograms; PN, personalized nutrition; UK, United Kingdom; US, United States



Chapter 8

A health technology assessment of personalized nutrition interventions using the EUnetHTA HTA Core Model

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ABSTRACT

Objectives

Poor nutrition links to chronic diseases, emphasizing the need for optimized diets. The EU-funded project PREVENTOMICS, introduced personalized nutrition to address this. This study aims to perform a health technology assessment (HTA) comparing personalized nutrition interventions developed through this project, with non-personalized nutrition interventions (control) for people with normal weight, overweight, or obesity. The goal is to support decisions about further development and implementation of personalized nutrition.

Methods

The PREVENTOMICS interventions were evaluated using the HTA Core model (EUnetHTA), which includes a methodological framework that encompasses different domains for value assessment. Information was gathered via [1] different statistical analyses and modeling studies, [2] questions asked of project partners and, [3] other (un)published materials.

Results

Clinical trials of PREVENTOMICS interventions demonstrated different body mass index changes compared to control; differences ranged from -0.80 to 0.20 kg/m^2. Long-term outcome predictions showed generally improved health outcomes for the interventions; some appeared cost-effective (e.g., interventions in UK). Ethical concerns around health inequality and the lack of specific legal regulations for personalized nutrition interventions were identified. Choice modeling studies indicated openness to personalized nutrition interventions; decisions were primarily affected by intervention's price.

Conclusions

PREVENTOMICS clinical trials have shown promising effectiveness with no major safety concerns, although uncertainties about effectiveness exist due to small samples (n=60-264) and short follow-ups (10-16 weeks). Larger, longer trials are needed for robust evidence before implementation could be considered. Among other considerations, developers should explore financing options and collaborate with policymakers to prevent exclusion of specific groups due to information shortages.

INTRODUCTION

Poor nutrition is a cause of chronic diseases such as ischemic heart disease (IHD), stroke, obesity, and type 2 diabetes (16,173). In 2019, dietary risk factors contributed globally to approximately 7.94 million deaths and 188 million disability-adjusted life years among people aged 25 years and older (15). Moreover, dietary factors account for approximately 18.2 percent of the costs associated with IHD, stroke and type 2 diabetes in the United States (16). Personalized nutrition has emerged as a promising field to address the limitations of current diet interventions and slow down the chronic disease pandemic (173). Since each individual has different nutrient needs and responses to diets, insights into these individual needs and responses can be leveraged to prevent, manage, and treat diseases and to improve health (431). Personalized nutrition has been defined by Ordovas et al. (23) as an approach that utilizes individual characteristics to provide targeted nutritional advice, products, or services. To develop such advice, products, or services, clinical assessments, biomarkers of physiological function and pathological processes, genetic information, and other available data derived from advanced technologies are needed (173).

While information on lifestyle and personal goals is commonly used to formulate personalized nutrition advice, the same is not true for advanced technologies such as those involving metabolomics and genotypic data, despite their potential to improve health outcomes (36,372). One project that explored the potential of advanced technologies in people with a normal weight, overweight and obesity is PREVENTOMICS, a recently completed European Horizon 2020 project (41), which investigated the potential of omics (especially metabolomics) as an input for personalized nutrition advice (8). By combining phenotypic characterization at the metabolomic level with a person's genotype, lifestyle, health status, preferences, and physiological status, a novel platform was developed and integrated into third-party applications. This integration resulted in three PREVENTOMICS interventions (8), which included the following: [1] integration of the platform for personalized food delivery, [2] integration of the platform at the retailer level for personalized recommendations when shopping, and [3] integration of the platform with a software to support healthcare professionals with formulating personalized dietary plans for consumers (42).

Decisions regarding the implementation of new approaches in healthcare such as PREVENTOMICS are rarely simple (432). Growing pressure on healthcare budgets has resulted in increased scrutiny of the overall value of new health technologies and programs (71). In this context, the importance of conducting a health technology assessment (HTA) is emphasized. HTA is a "multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" (72). "Value" includes different dimensions, such as clinical effectiveness, safety, costs, ethical and legal issues. HTA promotes transparency and accountability in government performance, and it can also help developers of new technologies in understanding how their technology will be assessed (i.e., early HTA);

by conducting such an "early HTA", the time and financing required for their product to gain market entry or get reimbursed can potentially be reduced (73,74).

Previous HTAs have often assessed only the costs, health effects, and cost-effectiveness of nutrition interventions, and have not systematically examined a wider range of possible issues relating to healthcare and society (75). To overcome the variance in the extent and scope of HTA, and the differences in reporting of the results, the European Network for HTA (EUnetHTA) developed the HTA Core Model (76). Conducting an (early) HTA with the HTA Core Model offers advantages such as the identification of key assessment components of interventions, the provision of a structured analysis of (early) scientific evidence, and the highlight of existing gaps from which the recommendations for subsequent decision-making steps can be formulated (77). Despite these benefits, only a limited number of studies utilizing the HTA Core Model for HTA have been published in scientific journals (331,433,434), and none of them were conducted in the nutrition field. As we believe that assessing the PREVENTOMICS interventions with the HTA Core Model in the premarket phase can help to inform further development and potential implementation decisions, this study aimed to compare these interventions with non-personalized nutrition interventions for people with normal weight, overweight and obesity, on all of the domains found in the HTA Core Model.

MATERIALS AND METHODS

General information regarding the HTA Core Model

The PREVENTOMICS interventions were evaluated using the HTA Core model developed by EUnetHTA, which has nine domains covering all aspects of an HTA (see Table 8.1) (78). This model was chosen because of its methodological framework for producing and sharing HTA information (78). Alternative frameworks were evaluated but not selected for various reasons. For example, the ISPOR Value Flower which offers a broader perspective on factors contributing to value in healthcare was not chosen because it predominantly centers on the concept and measurement of value rather than on the process and execution of HTA (435). The methodological framework of the HTA Core Model includes three components: [1] an HTA ontology including standardized questions (i.e., assessment elements) organized within a framework featuring nine domains that encompass all aspects that may be relevant for HTA and thereby value assessment, [2] methodological guidance, and [3] a common reporting structure. We used the first two components of the framework wherever possible. We did not use the common reporting structure and instead provided a summary of the relevant information per domain related to the PREVENTOMICS interventions, which gives a streamlined and accessible documentation of essential information. We believe that this is sufficient for stakeholders who are interested in further development or in taking (decision-making) steps regarding the implementation of the interventions.

Table 8.1: Different domains of the HTA Core Model, including the related methodology and sources used to address the domain.

Domains of HTA		Domain description as summarized in this study This domain summarizes (332):	Deliverable(s) (D) used[a]	Other sources
1	Health problem and current use of technology	• Target conditions + societal and individual burden of these conditions • Study populations • Current management. Knowledge is crucial for contextualizing and understanding outcomes observed in the other domains.	D1.2 ("Consumers Report") (published)[b] D7.5 ("Final plan for the Use and Dissemination of Results-PUDR")	Ghelanie et al. 2020 (436) Keijer et al. (8) OECD 2019 (11) PREVENTOMICS website (41)
2	Description and technical characteristics of technology	• Technical characteristics (e.g., users of the technologies) • Materials and equipment • Staff needed (and its training) • The regulatory status (i.e., the reimbursement policies of the technologies) Since even minor variations in technologies may result in different outcomes, this domain is of great importance.	D4.1 ("PREVENTOMICS platform design") D5.3 ("Report on the outcome of each intervention study") D7.5 ("Final plan for the Use and Dissemination of Results-PUDR") D9.1 ("Requirement N°1-Humans Interventional studies ")	Aldubayan et al. 2022 (47) Aldubayan et al. 2022 (46) Bothos 2022 (42) Bush et al. 2020 (173) Calder 2021 (44) Del Bas 2022 (45) Gerke et al. 2020 (437) Keijer et al. (8) Malczewska-Malec 2022 (43) Poley 2015 (321) PREVENTOMICS website (41) Van Berlo 2022 (340)
3	Safety	• Safety issues (unwanted or harmful consequences) that are important to participants • Or otherwise likely to be important in guiding decisions of stakeholders This could be related to occupational, and environmental safety.	-	Klingler et al. 2012 (438) NIDDK 2017 (439) Via questions asked via email to partners of the PREVENTOMICS project, who are experts in this field.
4	Clinical effectiveness	Health benefits including: • Mortality • Morbidity • Quality of life	D5.3 ("Report on the outcome of each intervention study") D5.4 ("Overall performance of PREVENTOMICS service") D6.4 ("Cost-effectiveness analyses results")	Aldubayan et al. 2022 (47) Clamp and Baker 2022 (440) Galekop et al. 2022 (441) Galekop et al. 2023 (442) Galekop et al. 2023 (443) Hoogendoorn et al. (281) Malczewsk-Malec et al. 2022 (444) Rabassa et al. 2022 (445)

Table 8.1: Continued.

Domains of HTA		Domain description as summarized in this study This domain summarizes (332):	Deliverable(s) (D) used[a]	Other sources
5	Costs and economic evaluation	• Costs • Health outcomes • Economic efficiency information Crucial given rising healthcare costs and limited healthcare budgets.	D5.3 ("Report on the outcome of each intervention study") D6.4 ("Cost-effectiveness analyses results")	Galekop et al. 2022 (441) Galekop et al. 2023 (442) Galekop et al. 2023 (443) Hoogendoorn et al. (281)
6	Ethical aspects	Social and moral norms and values, such as: • Benefit-harm balance • Autonomy • Respect for persons • Justice and equity • Legislation • Ethical consequences of the HTA Important to assess since moral values and norms, being the foundation of social life, significantly influence the way in which PREVENTOMICS interventions can be used in practice.	D1.2 ("Consumers' report") (published)[b] D7.2 ("Data management plan")	Mathers 2019 (446) Via questions asked via email to partners of the PREVENTOMICS project, who are experts in this field.
7	Organizational aspects	Mobilizing and organizing resources, including human skills and material artefacts, needed for implementation. Done by focusing on: • Healthcare system structure and delivery process • Management • Culture • Implementation challenges and barriers	-	Via questions asked via email to partners of the PREVENTOMICS project, who are experts in this field.
8	Patients and Social aspects	Issues for: • Individuals[c] • Caregivers • Social groups Understanding individual perspectives is crucial as they provide unique insights into experiences, attitudes, preferences, values, and expectations.	D1.2 ("Consumers' report") (published)[b] D5.3 ("Report on the outcome of each intervention study") D6.4 ("Cost-effectiveness analyses results")	Farrell et al. 2021 (447) Harris et al. 2023 (448) Galekop et al. 2023 (449)

Table 8.1: Continued.

Domains of HTA		Domain description as summarized in this study This domain summarizes (332):	Deliverable(s) (D) used[a]	Other sources
9	Legal aspects	• Individual's autonomy • Privacy • Health equality Rules and regulations protecting participant rights and societal interest.	D6.1 ("Ethical framework") D6.2 ("Regulatory framework") D7.2 ("Data management plan") D7.4 ("PUDR") D7.5 ("Final plan for the Use and Dissemination of Results-PUDR")	Ahlgren et al. 2013 (450) European Commission 2023 (451) Rottger-Wirtz & De Boer 2021 (452)

D, Deliverable; HTA, Health Technology Assessment; PREVENTOMICS, Empowering consumers to PREVENT diet-related diseases through OMICS sciences.
[a] All results were part of D6.5 ('Health Technology Assessment')
[b] Published online: https://preventomics.eu/deliverables/#1593502709004-84c73ce5-2fe4
[c] In this regard, "patient" and "individual" denotes those receiving a technology. This study focused on people without chronic diseases, and therefore the term "Individual" (or "participant") was used in this HTA.

Domain specific methods

Table 8.1 gives an overview of all domains, the description of the domains and the different sources used to gather information. A summary of domain-specific methods is given below. In general, information for the different domains was gathered via [1] different statistical analyses (i.e., analyses of health outcomes and questionnaires) and modeling studies (i.e., cost-effectiveness modeling and choice modeling); [2] questions asked via email to partners of the PREVENTOMICS project, who are experts in this field; or [3] other (un)published materials. Published materials included literature published in scientific journals, PREVENTOMICS blog posts and presentations. Unpublished materials included project deliverables (D). These deliverables are also known as supplementary outcomes (such as information, specialized reports, or brochures) that were required to be generated at a specific time throughout the project (453). All published materials related to the PREVENTOMICS project can be accessed on the website (41) and information about the referenced deliverables is provided in Appendix 8.1.

In most domains, (un)published materials were used as input, as well as the questions that were asked of the project partners (see Table 8.1). Additionally, clinical trial data were used as input for the "clinical effectiveness" and "cost and economic evaluation" domains and were analyzed using statistical methods (see footnote Table 8.3 for more details), with some results extrapolated over a lifetime. Although some of these results were already published elsewhere (47,441–443), we provided a summary of the trial-based effectiveness on dietary intake (i.e., Mediterranean Diet Adherence Score (MEDAS)), anthropometrics (i.e., body fat,

waist circumference and body mass index (BMI)) and QoL (assessed with the EQ-5D-5L and the Obesity and Weight Loss Quality of Life (OWLQOL)) (285,454).

The Markov obesity model with a 1-year cycle length was used to analyze data over a lifetime horizon and had different health states: diabetes, IHD, stroke, and death (see Figure 8.1 for the model structure) (281). The model simulated the disease occurrence for an obese cohort based on various inputs (e.g., population demographics and trial-based effectiveness on BMI). The effectiveness measure was quality-adjusted life years (QALYs) and the cost-effectiveness was expressed in the incremental cost-utility ratio (ICUR). More details about the model and inputs can be found elsewhere (281). Detailed lifetime results were published elsewhere (441–443) and summarized in this study.

Input for the "patients and social aspects" domain was supplemented with a validated diet satisfaction questionnaire (DSat-28 (© Laboratory for the Study of Human Ingestive Behavior, The Pennsylvania State University)), that assesses satisfaction with weight-management diets (455). The DSat-28 consists of 28 items with five response options ranging from "disagree strongly" to "agree strongly". The total score was calculated by averaging the summed score; higher scores indicate greater diet satisfaction. Additionally, preferences regarding personalized nutrition interventions were obtained from results from two published discrete choice experiments (DCEs) (449), that assessed preferences about [1] personalized nutrition advice and [2] personalized meals. More information about the methodology of these DCEs can be found elsewhere (449).

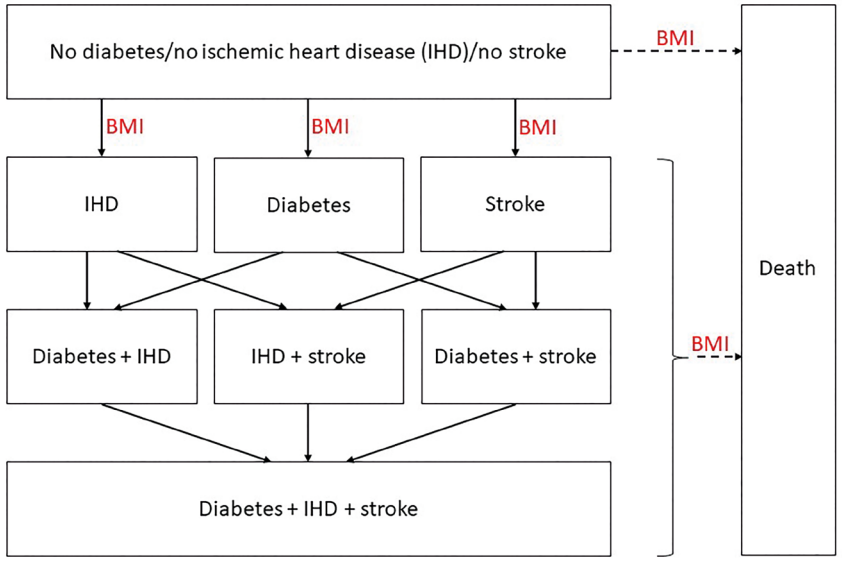


Figure 8.1: Structure of the Markov model for obesity as presented by Hoogendoorn et al. (281). BMI, body mass index; IHD Ischemic heart disease.

RESULTS

Health problem and current use of technology

The PREVENTOMICS interventions were used in four countries (Denmark, the United Kingdom (UK), Poland and Spain) targeting overweight and obese populations (41). Spain also included individuals with normal weight (see Appendix 8.2 for obesity classification by BMI). All interventions aimed to prevent diet-related diseases and improve health (41). More details can be found in Table 8.2.

The burden of obesity is high; in 2016, over half of the population in OECD countries was overweight and nearly one in four had obesity (11). Poor diet significantly contributes to this obesity epidemic, with almost half the population not meeting healthy diet guidelines and international standards. Overweight and related co-morbidities reduce average life expectancy in OECD countries by 2.7 years on average (11). Moreover, overweight and obesity result in an economic burden due to increased healthcare costs and reduced productivity. Over the next 30 years, OECD countries are projected to spend an average of 8.4 percent of their health budget on overweight-related problems, leading to a 3.3 percent reduction in gross domestic product due to obesity (11).

Although countries have implemented policies to tackle overweight and obesity, their success has been limited (11). Improvements in specific strategies such as mobile apps to promote healthier lifestyles could potentially tackle overweight and obesity. One study (D1.2 ("Consumers Report")) and the literature (436) found that many mobile apps for this purpose already exist. However, as far as we know, PREVENTOMICS uses a unique approach by applying new technologies (see "description and technical characteristics of the technology" domain) (8).

Table 8.2: Details on the PREVENTOMICS interventions, including information on the different intervention arms, study population and target condition.

Intervention				Study population	Target condition
Country	*General information*	*Intervention group(s)*	*Control group*		
Denmark(46)	Platform used in the elaboration and delivery of personalized food. Integrated with the SimpleFeast app. Trial period: 10-week randomized trial. Meals: vegetarian meals (breakfast and dinner) for 6 days. For the seventh day (Saturday) and for lunches, people needed to prepare meals themselves. They were allowed to eat non-vegetarian food, but were encouraged to refer to the recipe recommendations presented through the SimpleFeast App.	Personalized dietary plan (PP) Personalized easy-to-prepare meal boxes: based on metabolome and genetic analyses, participants were clustered into different groups and receiving group-specific meals. + functional ingredients matching the cluster were added to meals (47) + behavior change program[a]	General dietary plan General easy-to-prepare meal boxes. + behavior change program* (however do's were not personalized and were more informational messages).	Adults aged 18-65 years, with a BMI of 27-40 kg/m^2 and elevated waist circumference (men>94 cm; women>80 cm). No chronic diseases such as diabetes, heart diseases or cancer.	Improved diets result in a greater reduction in excess body fat and weight, as well as benefits in overall health in people with overweight and obesity. This could prevent diet-related diseases such as cardiovascular diseases, diabetes, several cancers, and stroke (194).
Spain (45)	Platform used at shop level. Integrated with the ALDI app (i.e., microsite). Trial period: 21-week parallel, randomized, placebo-controlled trial, and single-blind intervention trial. Division into study arms: Based on participants metabolome (urine, plasma, and serum samples) and saliva analysis of different single nucleotide polymorphisms, participants were randomized in a cluster, and divided into one of the three study arms.	Personalized nutrition (PN) Personalized recommendations through the ALDI catalogue. Personalized dietary plan (PP) PN + behavior change program[a]	General dietary plan Recommendations through the ALDI catalogue.	Adults aged 18-65, with a BMI of 18.5-35 kg/m^2 (general population including those living with obesity), without any chronic disease with clinical manifestation.	Improved dietary habits, measured through the adherence to the Mediterranean diet for people with- and without overweight and obesity, could lead to prevention of different diet-related diseases. This prevention could be [1] via overweight/obesity: reducing weight could prevent high blood pressure, elevated blood lipids, prediabetes and thereby prevent diet-related diseases (456), or [2] not via overweight/obesity: reduction in high blood pressure because of better nutrition (improvements in Mediterranean diets) might lead to prevention of diseases (10).

Table 8.2: Continued.

Intervention				Study population	Target condition
Country	*General information*	*Intervention group(s)*	*Control group*		
Poland/ UK (43,44)	Platform used through an upgraded ICT-based software for professionals. Integrated with the MetaDieta app. Trial period: 4-month single-blind randomized, placebo-controlled trials. Division into study arms: Based on participants classical biomarkers (urine, plasma, and serum samples) and saliva analysis (genetic polymorphisms) participants were allocated in a cluster and divided into one of the three study arms.	Personalized nutrition (PN)[b] Personalized diet created by a dietitian via a MetaDieta software. Participants themselves could also use the MetaDieta mobile app to support dietary compliance, monitor intake and contact the dietitian. Personalized dietary plan (PP)[b] PN + behavior change program[a]	General dietary plan Dietary plans were based on general healthy eating guidelines.	Adults aged 18-65 years, with a BMI of 25-40 kg/m2 and elevated waist circumference (men>94 cm; women>80 cm). People without any chronic diseases or treated with drugs could be included; however, people with hypertension and taking antihypertensive drugs (metabolically neutral) could be included.	The aim of the trial was to reduce weight and waist circumference by improving diets and to get favorable changes in metabolic profile. In turn, this might result in a reduction of abdominal obesity and the related diseases (194).

[a] Behavioral change program: delivered via ONMI (https://www.onmi.design/preventomics). Participants received 2-3 do's (behavioral prompts) per week. In nature, participants were prompt to take a specific action. The do's in the PP group were based on participants' reports from the behavioral questionnaire at baseline and inputs from nutritional recommendations. ALDI, supermarket; BMI, body mass index; cm, centimeter; ICT, information, and communication technology; kg, kilogram; m, meter.
[b] In this chapter, the intervention previously labeled as "PP+B" in both Poland and the UK (as described in Chapter 1, Chapter 5, and Chapter 9 of this PhD thesis) is now referred to as "PP". Conversely, the intervention previously known as "PP" in these countries is now labeled as "PN" in this chapter.

Description and technical characteristics of the technology

The PREVENTOMICS interventions assessed in this HTA involved the use of a platform in different ways. In general, the platform used relevant algorithms and analytics services to analyze user data (genetic, biological, nutritional, psychological) and stored it for providing personalized nutrition recommendations (8). These recommendations were transmitted through three different dietary apps: SimpleFeast, ALDI, and MetaDieta.

In more detail, the first PREVENTOMICS intervention integrated the platform with the SimpleFeast app for personalized meal delivery in Denmark (42,46,47). The second intervention integrated the platform at the retailer level with an ALDI supermarket app in Spain (developed ad hoc), which enabled customers to read personalized food product recommendations while grocery shopping (42,45). The third intervention integrated the platform with the MetaDieta app, designed for use by dietitians and study participants in the UK and Poland (42–44). Dietitians used this app to prepare diet plans and share them with the participants. Moreover, all interventions included a behavioral change program (340). See Table 8.2 for additional intervention details, Appendix 8.3 for the PREVENTOMICS user journey, Appendix 8.4 for required training and tools, and Appendix 8.5 for the study designs.

Reimbursement policies for nutrition-related technologies vary both across and within countries. Generally, nutrition interventions or related areas such as digital health tools are not reimbursed (173,321). However, recent initiatives, such as the introduction of the Digital Healthcare Act (Digitale-Versorgung-Gesetz) in Germany, aim to improve healthcare through digitalization and innovation by reimbursing tools such as obesity apps (437). See Appendix 8.6 for examples of reimbursement policies for different areas related to the PREVENTOMICS interventions in different countries.

Safety

PREVENTOMICS interventions are generally safe for individuals; no specific safety risks are related to the use of digital tools (a major component of the interventions). However, other activities related to the interventions may have safety hazards. For example, drawing blood (1-2 times per year) may cause minor bruising at the puncture site. Moreover, there is a risk of contamination due to improper needle management. To address these concerns, alternatives such as skin monitors for blood glucose measurement (439) or finger pricks (for small blood volumes) (438) can be used. In addition, there is a theoretical possibility that participants could receive the wrong type of personalized nutrition. However, manual checks minimize this risk. Moreover, since all dietary plans are based on the Mediterranean diet, recognized as a healthy diet, any potential error would have limited impact on health outcomes. The interventions do not pose risks to environmental or occupational safety.

Clinical effectiveness

To summarize the effectiveness of the PREVENTOMICS interventions, both short-term effectiveness (trial-based effectiveness) and long-term effectiveness (modeling trial-based

effectiveness over lifetime) were studied (see Table 8.3) and varied by intervention and country. In both intervention groups (PP and PN: see Table 8.2 for description) and the control, we observed short-term changes in health outcomes, including shifts in BMI and utilities (i.e., quality of life score) from baseline to follow-up. These shifts were generally associated with improved health (i.e., decreased BMI and improved EQ-5D-5L utilities); BMI change ranged from -1.31 kg/m^2 (PP group, UK) to 0.08 kg/m^2 (control, Spain) and utility change ranged from -0.02 (control, Denmark and UK) to 0.06 (PN, UK). Additionally, these changes from baseline to follow-up in PP and PN groups were compared with those in the control group, providing estimates of the difference in effectiveness between interventions and control, accompanied with 95 percent confidence intervals (CIs). The highest (statistically significant) effect on BMI was measured when PN was compared with control in Spain (-0.53 kg/m^2) and in utilities when PP was compared with control in Denmark (0.04). Notably, we observed contrasting effectiveness results in BMI in Poland when PN was compared with control; BMI in the control group decreased more than in the PN group, resulting in a +0.20 kg/m^2 difference. Analysis of the OWLQOL indicated significant increases in QoL for all PP and PN interventions compared to baseline (e.g., PP in Denmark: +3.85 (SE:1.67)). However, statistically significant differences in OWLQOL between interventions were generally not observed in most countries, except for PN versus control in Poland.

Predicting long-term outcomes based on short-term effects on BMI and utilities revealed that generally both PP and PN interventions led to improved lifetime health outcomes compared to the control group, translating into potential benefits such as fewer years with diabetes, increased life expectancy and lifetime health (QALYs). However, as Poland showed contrasting effectiveness results over the trial period, PN also had worse lifetime health outcomes compared to control (e.g., -0.015 QALYs) in base-case scenario. Scenario analyses, using the lower 95 percent confidence limit of short-term effectiveness on BMI (i.e., -0.45 kg/m^2), revealed increased QALYs for PN compared to control (+0.032), consistent with findings in other countries. More details on health outcomes can be found in Table 8.3 and in published materials (47,440–445).

Table 8.3: Trial and model outcomes related to (discounted) effects, costs, and cost-effectiveness.

		PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Effects trial period (baseline vs. follow-up)[a]						
Denmark	BMI, in kg/m^2 (mean, SE or CI)	-1.05 (0.17)[b]	-	-0.98 (0.15)[b]	-0.07 (-0.51, 0.38)	-
	Body fat, % (mean, SE or CI)	-1.0 (0.2)[b]	-	-0.9 (0.2)[b]	-0.1 (-0.7, 0.5)	-
	EQ-5D-5L utilities[f], (mean, SE or CI)	0.02 (0.01)	-	-0.02 (0.01)	0.04 (0.00, 0.07)[c]	-
	OWLQOL (mean, SE or CI)	3.85 (1.67)[d]	-	2.58 (1.56)	1.27 (-3.20, 5.75)	-
	DSAT-28[g], (mean, SE or CI)	0.24 (0.05)[b]	-	0.17 (0.05)[b]	0.07 (-0.08,0.27)	-
Spain	BMI, in kg/m^2 (mean, SE or CI)	-0.38 (0.13)[b]	-0.45 (0.14)[b]	0.08 (0.15)	-0.46 (-0.85, -0.07)[c]	-0.53 (-0.94, -0.13)[c]
	MEDAS, (mean, SE or CI)	2.80 (0.25)[b]	2.72 (0.27)[b]	3.01 (0.30)[b]	-0.22 (-1.00,0.55)	-0.29 (-1.08, 0.50)
	EQ-5D-5L utilities[f], (mean, SE or CI)	-0.00 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.01 (-0.04, 0.01)	0.00 (-0.02, 0.03)
	DSat-28[g], (mean, SE or CI)	0.13 (0.06)[d]	0.17 (0.07)[d]	0.25 (0.07)[b]	-0.12 (-0.30, 0.06)	-0.09 (-0.27, 0.10)
Poland	BMI, in kg/m^2 (mean, SE or CI)	-1.03 (0.23)[b]	-0.63 (0.22)[b]	-0.82 (0.24)[b]	-0.20 (-0.86, 0.45)	0.20 (-0.45, 0.85)
	Waist circumference, cm (mean, SE or CI)	-4.34 (0.77)[b]	-4.60 (0.74)[b]	-3.65 (0.80)[b]	-0.69 (-2.87, 1.48)	-0.95 (-3.09, 1.19)
	EQ-5D-5L utilities[f], (mean, SE or CI)	-0.00 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.01 (-0.04, 0.02)	0.00 (-0.03, 0.03)
	OWLQOL (mean, SE or CI)	7.75 (1.99)[b]	12.76 (1.91)[b]	5.91 (2.00)[b]	1.84 (-3.68, 7.37)	6.85 (1.43, 12.27)[c]
	DSat-28[g], (mean, SE or CI)	-0.03 (0.06)	0.16 (0.06)[b]	0.13 (0.06)[d]	-0.16 (-0.32, -0.00)[c]	0.03 (-0.13, 0.18)
UK	BMI, in kg/m^2 (mean, SE)	-1.31 (0.27)[b]	-0.84 (0.27)[b]	-0.51 (0.31)	-0.80 (-1.60, 0.00)	-0.33 (-1.14, 0.48)
	Waist circumference, cm (mean, SE or CI)	-8.80 (0.91)[b]	-6.63 (0.93)[b]	-1.6 (1.05)	-7.20 (-9.91, -4.48)[e]	-5.03 (-7.78, -2.28)[e]
	EQ-5D-5L utilities[f], (mean, SE or CI)	0.01 (0.03)	0.06 (0.02)[b]	-0.02 (0.04)	0.03 (-0.07, 0.13)	0.08 (-0.02, 0.17)
	OWLQOL (mean, SE or CI)	22.4 (4.49)[b]	11.63 (4.60)[d]	12.4 (5.18)[d]	10 (-3.44, 23.44)	-0.77 (-14.36, 12.82)
	DSat-28[g], (mean, SE or CI)	0.41 (0.12)[b]	0.32 (0.13)[d]	0.36 (0.14)[d]	0.05 (-0.32, 0.41)	-0.04 (-0.41, 0.33)

Table 8.3: Continued.

		PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Effects lifetime period[h]						
Denmark	Life years (base case)[i]	17.766	-	17.763	0.003	-
	Life years with diabetes (base case)[i]	2.769	-	2.781	-0.012	-
	Life years (scenario)[j]	17.784	-	17.763	0.021	-
	Life years with diabetes (scenario)[j]	2.698	-	2.781	-0.082	-
	Cum. Incident cases IHD/1000 (base case)[i]	279.448	-	279.788	-0.34	-
	Cum. Incident cases stroke/1000 (base case)[i]	315.719	-	316.094	-0.375	-
	Cum. Incident cases IHD/1000 (scenario)[j]	277.332	-	279.788	-2.455	-
	Cum. Incident cases stroke/1000 (scenario)[j]	313.381	-	316.094	-2.713	-
	QALYs (base case)[i]	15.117	-	15.106	0.011	-
	QALYs (scenario)[j]	15.139	-	15.106	0.033	-
Spain	Life years (base case)[i]	23.326	23.326	23.324	0.002	0.002
	Life years with diabetes (base case)[i]	1.38	1.374	1.416	-0.037	-0.042
	Life years (scenario)[j]	23.327	23.327	23.324	0.003	0.003
	Life years with diabetes (scenario)[j]	1.35	1.343	1.416	-0.067	-0.074
	Cum. Incident cases IHD/1000 (base case)[i]	148.732	148.537	150.016	-1.284	-1.479
	Cum. Incident cases stroke/1000 (base case)[i]	230.06	229.816	231.669	-1.609	-1.854
	Cum. Incident cases IHD/1000 (scenario)[j]	147.649	147.4	150.016	-2.367	-2.616
	Cum. Incident cases stroke/1000 (scenario)[j]	228.695	228.38	231.669	-2.974	-3.289
	QALYs (base case)[i]	20.158	20.162	20.156	0.002	0.006
	QALYs (scenario)[j]	20.162	20.166	20.156	0.006	0.01

Table 8.3: Continued.

		PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Poland	Life years (base case)[i]	19.385	19.36	19.372	0.013	-0.013
	Life years with diabetes (base case)[i]	2.865	2.952	2.908	-0.043	0.044
	Life years (scenario)[j]	19.425	19.4	19.372	0.053	0.028
	Life years with diabetes (scenario)[j]	2.73	2.813	2.908	-0.179	-0.096
	Cum. Incident cases IHD/1000 (base case)[i]	326.253	328.0997	327.171	-0.919	0.926
	Cum. Incident cases stroke/1000 (base case)[i]	409.089	412.369	410.721	-1.632	1.648
	Cum. Incident cases IHD/1000 (scenario)[j]	323.266	325.113	327.171	-3.905	-2.058
	Cum. Incident cases stroke/1000 (scenario)[j]	403.809	407.07	410.721	-6.913	-3.651
	QALYs (base case)[i]	16.536	16.51	16.525	0.011	-0.015
	QALYs (scenario)[j]	16.585	16.557	16.525	0.057	0.032
UK	Life years (base case)[i]	19.796	19.776	19.762	0.034	0.014
	Life years with diabetes (base case)[i]	1.552	1.596	1.627	-0.075	-0.031
	Life years (scenario)[j]	19.828	19.810	19.762	0.066	0.048
	Life years with diabetes (scenario)[j]	1.483	1.522	1.627	-0.144	-0.105
	Cum. Incident cases IHD/1000 (base case)[i]	341.617	343.553	344.921	-3.304	-1.368
	Cum. Incident cases stroke/1000 (base case)[i]	340.409	342.263	343.577	-3.168	-1.314
	Cum. Incident cases IHD/1000 (scenario)[j]	338.354	340.225	344.921	-6.567	-4.696
	Cum. Incident cases stroke/1000 (scenario)[j]	337.294	339.079	343.577	-6.283	-4.498
	QALYs (base case)[i]	16.023	16.019	15.979	0.044	0.040
	QALYs (scenario)[j]	16.056	16.053	15.979	0.077	0.074

Table 8.3: Continued.

		PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Costs trial period[k]						
Denmark	Total costs, 2020 € (DKK)	7,402 (55,277)	-	5,653 (42,215)	1,749 (13,062)	-
Spain	Total costs, 2020 €	539	519	131	408	388
Poland	Total costs, 2020 € (Zloty)	612 (2,733)	592 (2,643)	307 (1.369)	305 (1,364)	285 (1,274)
UK	Total costs, 2020 € (pounds)	1.319 (1,175)	1,299 (1,157)	806 (718)	513 (457)	493 (439)
Costs lifetime period[h, k]						
Denmark	Total costs (base case)[i], 2020 € (DKK)	520,102 (3,884 ,138)	-	518,366 (3,871,175)	1,736 (12,963)	-
	Total costs (scenario)[j], 2020 € (DKK)	520,023 (3,883 ,548)	-	518,366 (3,871,175)	1,657 (12,373)	-
Spain	Total costs (base case)[i], 2020 €	349,955	349,921	349,631	323	290
	Total costs (scenario)[j], 2020 €	349,876	349,837	349,631	245	206
Poland	Total costs (base case)[i], 2020 € (Zloty)	89,627 (399,025)	89,712 (399,401)	89,373 (397,892)	254 (1,133)	339 (1,509)
	Total costs (scenario)[j], 2020 € (Zloty)	89,463 (398,294)	89,544 (398,653)	89,373 (397,892)	90 (402)	171 (761)
UK	Total costs (base case)[i], 2020 € (pounds)	336,292 (299,438)	336,194 (299,351)	335,645 (298,862)	647 (576)	549 (489)
	Total costs (scenario)[j], 2020 € (pounds)	336,417 (299,549)	336,326 (299,468)	335,645 (298,862)	772 (687)	681 (606)

Table 8.3: Continued.

		PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Cost-effectiveness[h, k]						
Denmark	ICUR (base case)[i, L], 2020 € (DKK)				158,798 (1,185,909)	-
	ICUR (scenario)[j, L], 2020 € (DKK)				49,626 (370,610)	-
Spain	ICUR (base case)[i, L], 2020 €				172,789	50,108
	ICUR (scenario)[j, L], 2020 €				43,562	21,401
Poland	ICUR (base case)[i, L],2020 € (Zloty)				22,915 (102,018)	Control dominates
	ICUR (scenario)[j, L],2020 € (Zloty)				1,596 (7,107)	5,373 (23,920)
UK	ICUR (base case)[i, L], 2020 € (pounds)				14,607 (13,006)	13,726 (12,222)
	ICUR (scenario)[j, L], 2020 € (pounds)				9,991 (8,896)	9,149 (8,146)

a Different statistical tests were performed. Generalized Estimation equations were used to analyze the EQ-5D-5L utilities and linear mixed models were used to quantify the differences in effects between the PP/PN and control of all other health outcomes.
b p<0.01 significantly change from baseline
c p<0.05 significant difference between groups
d p<0.05 significantly change from baseline
e p<0.01 significant difference between groups
f Quality of life score
g© Laboratory for the Study of Human Ingestive Behavior, The Pennsylvania State University
h Discounted results were presented
i Base-case: point estimates of BMI as observed from the trials were used as input in the model.
j Scenario: the lower level of the 95% confidence intervals from the effect in BMI were used as input in the model.
k All costs were then converted from 2020 national currency to 2020 Euros using the following exchange rates: 1 DKK = 0.134 Euro, 1 Zloty = 0.225 Euro, 1 pound = 1.123 Euro.
L WTP thresholds: Denmark; €47,817 per QALY gained (357,100 DKK), Spain; €30,000 per QALY gained, UK; €22,461 per QALY gained (20,000 pounds), Poland; €38,430 per QALY gained (171,092 Zloty).
* In this chapter, the intervention previously labeled as "PP+B" in both Poland and the UK (as described in Chapter 1, Chapter 5, and Chapter 9 of this PhD thesis) is now referred to as "PP". Conversely, the intervention previously known as "PP" in these countries is now labeled as "PN" in this chapter.
BMI, body mass index; CI, confidence interval; cm, centimeter; Cum, cumulative; DKK, Danish krone; DSAT; diet satisfaction questionnaire; EQ-5D, EuroQol five-dimension questionnaire; ICUR, incremental cost-utility ratio; IHD, ischemic heart disease; kg, kilogram; MEDAS, Mediterranean diet score; m, meter; OWLQOL, Obesity and Weight Loss Quality of Life; PN, personalized nutrition intervention; PP, personalized plan intervention; QALY, quality-adjusted life year; SE, standard error; UK, United Kingdom.

Costs and economic evaluation

The interventions (PP and PN) had higher costs compared to the control over the trial period, with Denmark showing the highest costs (see Table 8.3). Appendix 8.7 provides further details on the intervention costs. Over a lifetime horizon, costs were considered from an extended societal perspective, including obesity-related disease costs, unrelated medical costs, non-medical costs, informal care costs and productivity costs. In summary, lower costs related to diabetes, IHD and stroke were offset by higher costs in other areas (i.e., unrelated medical costs, non-medical costs, and informal care) due to increased life years resulting from the interventions. Depending on the chosen willingness to pay (WTP) threshold and the specific intervention (PP or PN), some interventions were deemed cost-effective, such as PP and PN in the UK and PP in Poland. Scenario analyses revealed additional cost-effective interventions, including PN in Spain and PN in Poland. See Table 8.3 and published materials (441–443) for more details. Given the high prevalence of overweight and obesity, personalized nutrition interventions would have a substantial budget impact.

Ethical aspects

This HTA included an examination of ethical issues. The PREVENTOMICS interventions demonstrated a favorable benefit–harm balance, as they showed no significant harms (safety domain) but some improvements in clinical effectiveness (effectiveness domain). Moreover, the interventions respect individual autonomy, human dignity, human rights and participants' privacy and integrity. However, health inequality may arise if these interventions are not reimbursed by a third party and may thus be necessary to prevent disparities between wealthier and poorer individuals. More specifically, lower-income individuals generally have poorer diets and higher disease burdens, while higher-income individuals have better access to the interventions (446). Additionally, older individuals may face challenges in using the interventions due to digital illiteracy or lack of suitable mobile phones. See Appendix 8.8 for more details.

Organizational aspects

In general, the PREVENTOMICS interventions were considered supplementary to the existing work processes of professionals such as nutritionists or dietitians. Professionals were likely to be familiar with the use of apps to document health behaviors but were asked to perform additional tasks related to genetic and metabolic sampling, which they usually do not do. Besides guidance on sampling for genetics and metabolomics, minimal training or education is expected (see Appendix 8.4). However, besides the comparable study design in the UK and Poland, the (cost)-effectiveness results were not consistent. One possible explanation is that the UK utilized a more didactic approach for providing recommendations, resulting in better outcomes. Providing training to professionals on delivering information may therefore optimize results.

Personalized nutrition requires that participants undergo tests, which might decrease their enthusiasm. However, an app to document food habits and other information could

help maintain their motivation. Overall, participants generally accepted the PREVENTOMICS interventions well, despite some difficulties in app usage, particularly in the UK and Poland. However, most problems were solved or had minimal impact. More details and examples can be found in Appendix 8.9.

Patients and Social aspects

Understanding the experiences of overweight or obese individuals is crucial for the success of PREVENTOMICS interventions. Farrell et al. (447) found that people with obesity experience negative issues, such as emotions, traumas, restrictions in movements, stigma, and lack of respect. The DSat-28 results indicated slight increases in diet satisfaction for almost all intervention groups compared to baseline (see Table 8.3). Additionally, a DCE study revealed willingness to choose personalized nutrition interventions, with total expenditure being the most important factor influencing peoples' preferences (449). Behavioral reminders were not highly valued. The DCE study also showed participation rates for specific scenarios, including scenarios somehow similar to PREVENTOMICS interventions and revealed rates varying from 26 percent to 49 percent across countries and interventions (449). Moreover, a UK cohort study revealed substantial variations in genetic testing preferences, which tests are also needed in personalized nutrition interventions, between white and ethnic minority individuals, with the white cohort being twice as likely to undergo genetic testing (448).

Gaining user trust is crucial for intervention success, emphasizing the importance of transparent and simple explanations of interventions and their benefits (D1.2. ("Consumers Report")). In the Danish trial, 50 percent of the participants were excited to be part of the study and inspired to eat more vegetarian-based food, but they also missed familiar meals and felt isolated (D5.3 ("Report on the outcome of each intervention study"). In the Spanish trial, participants criticized time-consuming shopping lists. In the UK and Poland, participants felt cared for by healthcare professionals, and some participants felt better during the dietary intervention than before. However, some mentioned that adhering to the diet was more time-consuming and expensive than their previous diet.

Legal aspects

Personalized nutrition lacks specific legal regulations due to its multifaceted nature (which includes aspects such as advice, testing and foods), making legislation fragmented (450,452). In other words, personalized nutrition interventions can be categorized as "health" or "lifestyle" intervention or "food" or "medicine", affecting the applicable rules and regulations (452). Röttger-Wirtz and De Boer (452) analyzed food laws and showed for example that, it is often unclear whether certain nutrigenomic or nutrigenetic effects should be classified as health optimizing, health maintaining, or disease preventive effects. Classifying it as disease preventive, results for example in regulating the intervention as a medicinal product, rather than governed by food laws.

There are legal requirements that apply to all personalized nutrition interventions, including the General Data Protection Regulation (GDPR) for personal data. GDPR guidelines were prioritized in the PREVENTOMICS interventions by ensuring anonymization. Moreover, CE marking is required under the current medical device regulation for the European market, as interventions like PREVENTOMICS are classified as in vitro diagnostic medical devices (IVD) (451). For more details, see Appendix 8.10.

DISCUSSION

This study aimed to assess the PREVENTOMICS interventions in a pre-market phase with the HTA Core Model to inform development and implementation decisions. Conducting an "early HTA" is an effective method to identify and address potential issues regarding market access and reimbursement (54). The different domains showed that approaches like PREVENTOMICS to reduce overweight and obesity are needed. Moreover, people express willingness to use these interventions (449), though certain groups (i.e., white individuals) exhibit higher likelihood of genetic testing than others (i.e., ethnic minority individuals) (448). Furthermore, our findings indicate that PREVENTOMICS interventions entail low safety risks and require minimal training. While their implementation may require some challenges at the organizational level, the trials showed that they are resolvable.

PREVENTOMICS interventions could have favorable effectiveness results; small short-term effects observed during the trials could translate into long-term health benefits (16,173). Results align with other studies; see Aldubayan et al. (47) for comparison of PREVENTOMICS effectiveness results with other studies. Additionally, Galekop et al. (280) found that personalized nutrition interventions often led to incremental QALYs between 0 and 0.1, comparable with our study findings. While the effects observed are small, most effects are clinically meaningful (requiring a minimum 0.03 difference in utility score) (457,458). However, in Spain, short-term effects resulted in minimal long-term benefits for both PP and PN interventions compared to control (incremental QALYs of 0.002 and 0.006, respectively), contrasting with other countries where incremental QALYs were at least 0.01. Between country differences may stem from the diverse interventions and populations, including cultural differences and targeted weight classifications. For example, Aune et al. (208) demonstrated a J-shaped relationship between BMI and all-cause mortality, potentially explaining the lower effect observed in Spain, which encompasses the general population, including those with normal weight, unlike other countries where studies focused on people with overweight and obesity.

Although clinical trials on technology-based and personalized nutrition interventions often feature small sample sizes and short follow-ups (36,459), leading to effectiveness and parameter uncertainties in cost-effectiveness analyses, Hogervorst et al. (460) suggested improving data quality and quantity to reduce uncertainty, which for PREVENTOMICS interventions could be achieved by longer and larger trials. Our cost-effectiveness analyses

explored the potential health benefits of the interventions in the scenario analyses and revealed promising cost-effectiveness results for the interventions in Spain, the UK and Poland.

The use of PREVENTOMICS interventions would likely increase both short-term and lifetime costs, which raises various questions. First, our findings support literature indicating that personalized nutrition is more often used by motivated and wealthier individuals (452), particularly when out-of-pocket payments are required. This raises ethical concerns, as personalized nutrition can exacerbate health inequality, given that individuals with lower socioeconomic status often have poorer diets and higher disease burdens but may struggle to afford these interventions (446). Therefore, third-party reimbursement for effective personalized nutrition interventions is crucial. However, budget constraints may prevent decision-makers to reimburse interventions for the whole target population. It may therefore be advisable to consider reimbursing effective personalized nutrition interventions only for sub-populations with the highest health or economic burden (e.g., severely obese) (254). Alternatively, partial subsidies could be provided, covering specific components of the interventions such as testing or mobile app costs.

Additionally, we recommend that stakeholders, such as policymakers, should collaborate to develop a cohesive legal framework that fosters consumer trust, engagement and enables personalized nutrition to reach its full potential (452,461). Furthermore, policymakers, together with developers, should focus on addressing the concerns of ethnic minority individuals, specifically regarding employment repercussions of genetic tests (448), ensuring inclusivity and avoiding exclusion due to information shortages. Moreover, despite the ending of the EUNetHTA Joint Actions by September 2023, collaboration on HTAs is recommended between countries to keep track of the fast-changing field of personalized nutrition and to produce timely HTA information for decision-makers. The new “regulation on HTA” is expected to support this future collaboration (462).

This HTA has several limitations. First, as the HTA Core Model was not designed for personalized nutrition interventions (332), additional domains or assessment elements may be needed. Becla et al. (463) highlighted the importance of ethical, organizational, social, and legal aspects in personalized healthcare and suggested rethinking the “gold standard” of large trials and instead considering “personal evidence”. Moreover, Von Huben et al. (464) identified inconsistencies in current HTA frameworks for digital health tools, suggesting the inclusion of digital-specific content in existing or new elements of the HTA Core Model. More specifically, potential additions to the HTA assessment of PREVENTOMICS interventions could be the consideration of device features like size, battery life, operating system, technical support, and connectivity (assessment element ID B0007 should be modified). Moreover, adding new assessment elements could be considered, for example DHT08 in the safety domain (464): “how well are updates/continuity of digital health technologies managed?” While we believe all essential aspects are covered in our HTA, future research should analyze more aspects for a more comprehensive overview of digital tools in personalized nutrition interventions.

Second, we obtained expert opinions in this HTA without a systematic approach and we did not fully follow the recommended EUnetHTA methodological framework. Nonetheless, we believe that our approach identified the most critical issues in personalized nutrition interventions.

Third, this HTA primarily focused on BMI as (short-term) outcome measures, but other health outcomes such as waist circumference, blood glucose, systolic blood pressure or LDL cholesterol might even be more important (194,325). However, there is limited literature on translating short-term changes in these outcomes into lifetime estimates of disease risk, health outcomes and costs (281).

In addition to previously mentioned future research suggestions, another recommendation is to extend this HTA by using multiple criteria decision analysis (MCDA) to systematically evaluate and rank ideas based on weighted criteria (465). Since MCDA can identify the relative importance of different criteria, this method can help to maximize societal value when resources are allocated (465).

CONCLUSION

In conclusion, our HTA emphasizes the relevance of evaluating personalized nutrition interventions beyond costs, effects, and economic aspects by addressing different (related) issues. While PREVENTOMICS interventions exhibit potential (cost)-effectiveness, developers should prioritize gathering additional evidence through longer and larger-scale trials. Addressing organizational issues and early discussions with third-party payers about reimbursement options are recommended for developers. Additionally, policymakers, together with developers, should work on collecting and providing accessible and comprehensive information (e.g., on genetic testing) for all ethnic groups. Moreover, a cohesive legal framework and a system-wide collaboration among stakeholders, including European HTA are needed, prior to making implementation decisions.

APPENDICES

Appendix 8.1: Deliverables

Table 8.1.1: (Reference) information of the deliverables used in the health technology assessment.

Deliverable name	Part of (1) work package (WP) and (2) task (T)	Actual date of delivery	Used in domain
Deliverable 1.2 ('Consumers Report') (published)*	WP1: Business modeling T1.2 Consumers and Business Requirements Alignment	31-07-2019	Health problem and current use of technology (CUR) Ethical analysis (ETH) Patients and Social aspects (SOC)
Deliverable 4.1 ('PREVENTOMICS platform design')	WP4: PREVENTOMICS personalized nutrition integration T4.1 PREVENTOMICS platform design and communication interfaces specification	31-10-2019	Description and technical characteristics of technology (TEC)
Deliverable 5.3 ('Report on the outcome of each intervention study')	WP5: Consumer-centered interventions T5.4: Deployment of the intervention	21-07-2022	Description and technical characteristics of technology (TEC) Clinical effectiveness (EFF) Costs and economic evaluation (ECO) Patients and Social aspects (SOC)
Deliverable 5.4: ('Overall performance of PREVENTOMICS service')	WP5: Consumer-centered interventions T5.5 Validation of the PREVENTOMICS approach and business cases	23-06-2022	Clinical effectiveness (EFF)
Deliverable 6.1 ('Ethical framework')	WP6: Regulatory, Economic and Health impact T6.1 Regulatory, Ethics and Gender aspects	29-04-2019	Legal aspects (LEG)
Deliverable 6.2 ('Regulatory framework')	WP6: Regulatory, Economic and Health impact T6.1 Regulatory, Ethics and Gender aspects	28-04-2020	Legal aspects (LEG)
Deliverable 6.4 ('Cost-effectiveness analyses results')	WP6: Regulatory, Economic and Health impact T6.3 Cost-effectiveness	25-07-2022	Clinical effectiveness (EFF) Costs and economic evaluation (ECO) Patients and Social aspects (SOC)

Table 8.1.1: Continued.

Deliverable name	Part of (1) work package (WP) and (2) task (T)	Actual date of delivery	Used in domain
Deliverable 7.2 ('Data management plan')	WP7: Market impact management and dissemination T7.4 Knowledge and Data Management	30-04-2019	Ethical analysis (ETH) Legal aspects (LEG)
Deliverable 7.4 ('PUDR')	WP7: Market impact management and dissemination T7.1 IPR Management and Exploitation	31-05-2020	Legal aspects (LEG)
Deliverable 7.5 ('Final plan for the Use and Dissemination of Results-PUDR')	WP7: Market impact management and dissemination T7.1 IPR Management and Exploitation	31-10-2021	Health problem and current use of technology (CUR) Description and technical characteristics of technology (TEC) Legal aspects (LEG)
Deliverable 9.1 ('Requirement N°1 – Humans - Interventional studies ')	WP9 Ethics requirements	26-07-2022	Description and technical characteristics of technology (TEC)

*Published online: https://preventomics.eu/deliverables/#1593502709004-84c73ce5-2fe4

Appendix 8.2: Obesity classification

Table 8.2.1: Obesity classification (466).

BMI (kg/m²)	Classification
<18.5	Underweight
18.5 to <25	Healthy weight
25.0 to <30	Overweight
30.0 or higher	Obesity
30 to <35	Class 1
35 to <40	Class 2
40 or higher	Class 3 (severe obesity)

Appendix 8.3: User Journey

Figure 8.3.1: PREVENTOMICS User Journey (42).

Appendix 8.4: Trainings and tools

Table 8.4.1: Summary of main findings on training and tools needed for PREVENTOMICs interventions.

	Country	Training	Tools
Participants (volunteers/ patients receiving intervention)	*Denmark*	No training required. However, it is good to highlight the importance of good food and to give them background information of personalized nutrition.*	Mobile phone, meals, internet connection
	Spain	No training required. However, it is good to highlight the importance of good food and to give them background information of personalized nutrition.*	Mobile phone, internet connection
	Poland/UK	When dietary recommendations are given by the dietitian/ nutritionist through the MetaDieta app, participants can use this app as well. Training for this app can be given by the dietitian/nutritionist, to make sure the participant understands it correctly.*	Mobile phone, internet connection
Professionals	*Denmark*	Training for SimpelFeast (or other companies that will use the intervention when it might be on the market). This might be about the background information of personalized nutrition, but also more technical stuff (e.g., how to integrate the PREVENTOMICS platform with the SimpleFeast app).**	All necessities for doing blood, urine, and saliva tests (needles, samples etc.). And all necessities for measuring all anthropometric measures (scale, measuring tape etc.).
	Spain	Training for Aldi professionals (or other supermarkets when they are interested in this intervention). This might be about the background information of personalized nutrition, but also more technical stuff (e.g., how to integrate the PREVENTOMICS platform with the ALDI app).**	
	Poland/UK	Training for nutritionists/dietitian about the use and importance of the application (e.g., lectures on genetic changes in obesity (see Deliverable 7.5 ('Final plan for the Use and Dissemination of Results-PUDR')).**	All necessities for doing blood, urine, and saliva tests (needles, samples etc.). And all necessities for measuring all anthropometric measures (scale, measuring tape etc.). Moreover, dietitian consultation rooms and all that is needed for this consultation (e.g., gloves).
Service exploitator (someone who can store and analyze the data).		Training on how to use and maintain the PREVENTOMICS platform. Moreover, how to integrate this with different business cases.	Computers, internet connection. Materials to analyze the data.

**Training might be needed if it is asked from the participants to take blood, urine, and salvia samples themselves.*
*** Training might be needed if professionals are asked to take the blood, urine, and salvia samples from the participants and if they are not used to do this.*

Appendix 8.5: Study designs

Figure 8.5.1: Study design Denmark (Deliverable 9.1 ('Human Interventional Studies')).

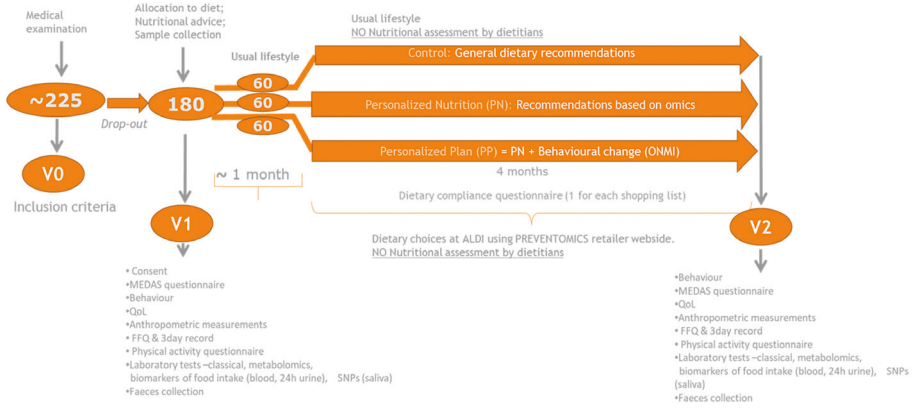


Figure 8.5.2: Study design Spain (Deliverable 9.1 ('Human Interventional Studies')).

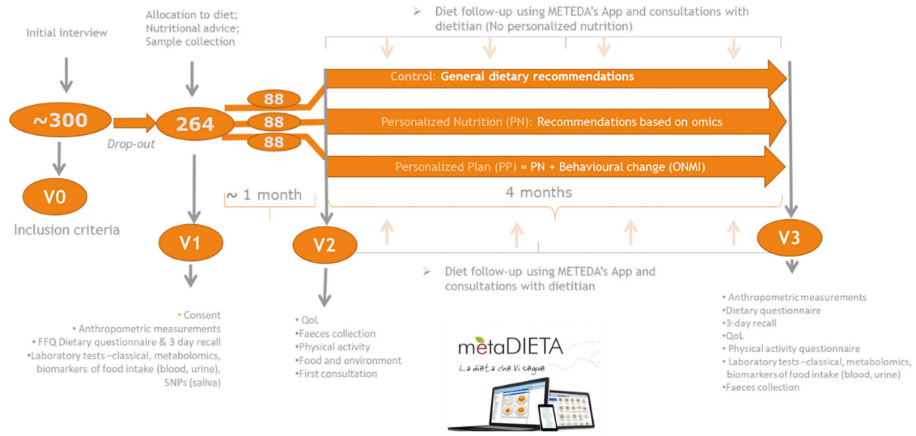


Figure 8.5.3: Study design Poland (Deliverable 9.1 ('Human Interventional Studies')).

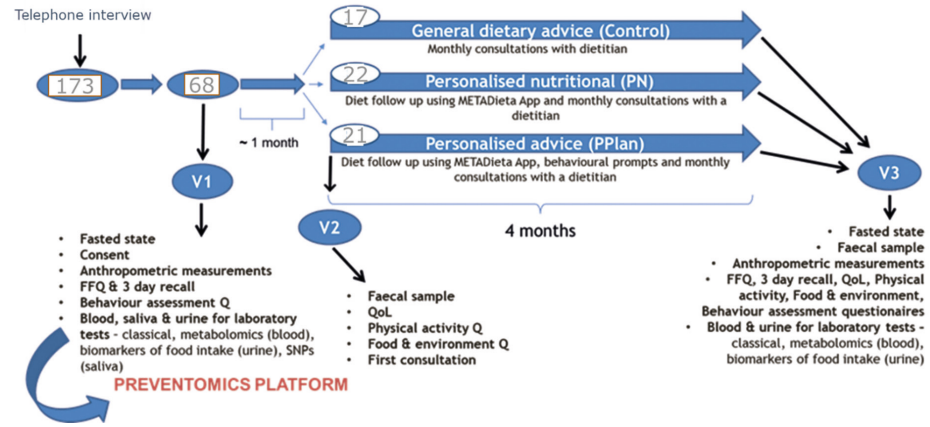


Figure 8.5.4: Study design UK (Deliverable 9.1 ('Human Interventional Studies')).

Appendix 8.6: Reimbursement

An overview of literature and other online sources on reimbursement regulations of personalized nutrition and related areas in Europe and the United States.

Since results of Health technology assessments (HTA) may eventually be used in making treatment guidelines or to inform policy makers in their reimbursement decisions (i.e., include or exclude a treatment in a benefits package) (321), it is important to say something about reimbursement in this HTA as well. Although there is increasing literature and information available on the HTA and reimbursement procedures about pharmaceuticals, there is often less known about these procedures for non-pharmaceuticals (467,468). Moreover, it is not only the procedure that is often unknown, non-pharmaceuticals, such as nutrition related products, are often not reimbursed at all. While there are examples of nutrition interventions that were reimbursed, food products and nutrition interventions are typically not reimbursed by a third-party payer (173,321). Instead, users need to pay out-of-pocket. In this appendix, we highlight several findings in the literature about the reimbursement of this type of interventions. Moreover, examples of related areas, such as medical nutrition, medical nutrition therapy (MNT) for diabetes type 2, lifestyle interventions, and digital health are given. It must be noted that the information provided below are specific examples in countries, but that each country has its national and local policies.

Medical nutrition

Medical nutrition is defined as food for special medical purposes/medical food by Perugini et al. (468), who studied the coverage and reimbursement of medical nutrition in different countries. It is not used for prevention purposes, but instead used to treat nutrition-related disorders and conditions such as malnutrition. It comprises two specific types: enteral nutrition and parenteral nutrition. Enteral nutrition includes oral nutritional supplements and enteral tube feedings into the digestive tract and its use is regulated via food for special

medical purposes/medical food. Parental nutrition is administered intravenously and is regulated by pharmaceutical legislation. It was found by Perugini et al. (468) that most countries have limited reimbursement/coverage for medical nutrition, especially in the outpatient/community setting. Moreover, these policies were often outdated or there was a lack of HTA on medical nutrition at all (i.e., France and Brazil were the only countries with formal HTA procedures) (468).

In Denmark, patients who receive nutritional therapy upon discharge are subject to the rules for dispensing pharmaceuticals (469). In the case of parenteral nutrition, reimbursement regulations are based on the clinical diagnosis rather than the patient's nutritional status. There is a lack of clarity regarding financial responsibility, including reimbursement for parenteral nutrition after discharge. Palliative care patients and those with short bowel syndrome have a designated reimbursement system, but it is unclear for other diagnoses (469).

Medical nutrition therapy (MNT)

A common approach in the prevention of type 2 diabetes is MNT (418), which is defined as "nutritional diagnostic, therapy, and counselling services for the purpose of disease management which are furnished by a registered dietitian or nutrition professional…"(418). In the US, a physician referral is needed to get MNT reimbursed by a payer like Medicare (national health insurance program). However, current procedural terminology and billing procedures for MNT vary and are interpreted differently by carriers and billing agencies, within government-funded programs and private sector insurance plans. Moreover, the US Preventative Services Task Force recommends screening for abnormal blood glucose to be part of cardiovascular risk assessments (418). This task force focuses on adults aged 40-70 years who are overweight or obese. If they are diagnosed with abnormal blood glucose, the clinician should offer them intensive behavioral counselling interventions to promote a healthy diet plan and increase physical activity. However, coverage is not guaranteed by all plans. Additionally, nutrition services, including diabetes education by registered dietitian nutritionists, are also often part of a bundled payment system in acute care settings. There is a growing adoption of alternative payment models in the US, which creates the opportunity to support nutrition services to prevent diabetes based on factors such as their cost-effectiveness (418).

In Poland, generally healthy people, or obese people without significant complications seek dietary advice, personalized or not, only in private facilities and at their own expense (354,355). Since October 2022, some patients can receive free dietary advice through the National Heath Fund. Eligible patients include diabetic patients, patients treated in cardiology, patients seen in pulmonary/allergy clinics, and patients with thyroid diseases.

Prevention in general, including lifestyle interventions

Overall, general practitioners in Europe experience a barrier to use health promotion in clinical practice (470). One of these main barriers is the lack of reimbursement in these activities. Participants in another study of obesity management in Europe (471) mentioned the need

for reimbursement of dietitians, physical activity professionals as well as psychologists and the need for better promotion of healthy lifestyles. Insurance companies need to be involved if there is no national health service that can provide what is needed.

A cross-sectional survey study of lifestyle medicine (LM) practitioners in the US (472) reported results that were similar to those found in the two above mentioned studies in Europe (470,471). LM is defined here as "a clinical discipline in which practitioners and the entire healthcare team treat many common non-communicable chronic diseases using health behavior change as the foundation of care". This could include interventions such as changing the eating pattern, regular physical activity, stress management and more. This study reported that 55% of practitioners were unable to receive reimbursement for their LM practice. Among the 471 survey respondents who answered the question about how to make LM practice easier, several suggestions were offered. Among others, these included: overall reimbursement, reimbursement for more time spent with patients and reimbursement for the extended care team (472).

Zwaagstra Salvado et al. (473) studied the links between reimbursement and prevention in the Netherlands. They found that there is not just one reimbursement scheme available that will stimulate all levels of prevention, but that different types of reimbursement work well for different preventive services. For example, prevention activities that are easy to specify could benefit from a volume incentive (as an example of fee for service). Interventions that are not easily specified, such as providing education on lifestyle factors, could better work with population-based capitation reimbursement.

One specific example of an intervention that is reimbursed for Dutch citizens with overweight or obesity per January 2019 is the combined lifestyle intervention (CLI) (474). These are multicomponent interventions lasting two years, consisting of interactive sessions with care professionals. Moreover, it is tailored to the participant's needs. More information can be found in the literature (474).

Digital health

The market of digital health solutions is a rapidly growing sector, but reimbursement from public payers is often lacking (380). More specifically, in the UK and the Netherlands, there is no national-level reimbursement framework for low-risk health apps (356). Individual trusts/CCGs can cover these kinds of apps in the UK and in the Netherlands individual insurance companies can cover apps or can jointly purchase them. Digital health solutions are currently not evaluated within an HTA framework in the Netherlands. However, in the UK, NICE has developed a digital health technology framework to assess digital health solutions (356). The UK also has an NHS Apps library, collecting all health apps that have been assessed against national standards and have been proven to be safe and secure. However, the addition of an app to this catalogue thus does not mean that funding or reimbursement will necessarily

follow. It is recommended that this link with funding, reimbursement and/or coverage increases (356).

Compared to other European counties, the pathway of reimbursement of digital solutions is quite mature in the UK (380). For example, in Spain there are numerous highly independent regional payers, each with their own unique reimbursement pathways and evidence requirements for digital solutions. This market is therefore a challenge to tackle (380).

In Germany, the parliament introduced the digital healthcare act (Digitales Versorgungsgesets, DVG) by the end of 2019 (475). This act describes a pathway for the reimbursement of digital health apps (i.e., digitale Gesundheitsanwendung, DiGA). In other words, 90% of the German population in insured by the statutory health insurance (SHI) and the DVG grants individuals with SHI the right to receive benefits for certain DiGA. This means that insurers will cover the expenses associated with utilizing these DiGA (437). However, coverage benefits will only be granted if the DiGA meets the following criteria (437,475):

1. Show a beneficial impact on healthcare, either through medical benefits or improvements in healthcare procedures and structures.
2. Categorized as a low-risk medical device (Class I or IIa) in accordance with medical device regulation (MDR).
3. Primarily operates based on digital technology.
4. Serves a medical purpose, such as monitoring, detecting, alleviating, or treating illnesses, or compensating, detecting, relieving, or treating injuries or disabilities for injured individuals or in healthcare provided by service providers.
5. Primarily centered around the patient.

In June 2023, there were already 53 DiGA applications approved for reimbursement (476). DiGAs that were approved focused on psychology, but other therapeutic areas included for example stroke, obesity, and diabetes (476).

Given these various health system structures, funding models, and regulations within and between countries, coupled with heightened scrutiny from payers, providers, and physicians, it is crucial for developers to invest significant time and effort in proving the effectiveness and efficiency of their new treatments if they hope to receive reimbursement on a large scale (380). It is recommended for future research to make a clear overview of reimbursement policies in different countries in Europe about all different areas related to personalized nutrition, by means of an extended literature search and/or online documents of the countries of interest.

Appendix 8.7: Intervention costs

Table 8.7.1: Danish trial: average intervention costs per participant (2020 €, (DKK)).

Components	PP	Control	Difference
Meals (breakfast & dinner, eaten 6 days per week)			
Direct costs			
Food costs	2,746 (20,507)	2,746 (20,507)	0
Packaging costs	1,239 (9,253)	1,239 (9,253)	0
Production costs	1,273 (9,507)	318 (2,375)	955 (7,132)
Delivery costs	189 (1,411)	189 (1,411)	0
Indirect costs (25% of direct costs)	1,362 (10,171)	1,123 (8,387)	239 (1,784)
Functional ingredients	5.00 (37.39)	0	5.00 (37.39)
Total meal costs	*6,814 (50,887)*	*5,616 (41,940)*	*1,198 (8,947)*
Behavioral messages via app	15 (112)	15 (112)	0
Access SF app recipes	21 (155)	21 (155)	0
PREVENTOMICS platform (storage data + questionnaires maintenance)	0.81 (6.02)	0.81 (6.02)	0
Tests (blood, urine, saliva)			
Omics	383 (2,857)	0	383 (2,857)
Genetics	54 (403)	0	54 (403)
Other (e.g., overhead)	115 (857)	0	115 (857)
Total tests costs	*550 (4,111)*	*0*	*550 (4,111)*
TOTAL COSTS	**7,402 (55,277)**	**5,653 (42,215)**	**1,749 (13,062)**

DKK, Danish Krone; PP, Personalized Plan; SF, Simple Feast.

Table 8.7.2: Spanish trial: average intervention costs per participant (2020 €).

Components	PP	PN	Control	Difference PP-Control	Difference PN-Control
Behavioral messages via app per participant	10	0	0	10	0
Behavioral message integration with ALDI microsite + maintenance	10	0	0	10	0
Extra costs grocery shopping (eating healthier)	130	130	130	0	0
PREVENTOMICS platform (storage data + questionnaires maintenance)	1.40	1.40	1.40	0	0

Table 8.7.2: Continued.

Components	PP	PN	Control	Difference PP-Control	Difference PN-Control
Tests (blood, urine, saliva)					
Omics	257	257	0	257	257
Genetics	54	54	0	54	54
Other (e.g., overhead	77	77	0	77	77
Total tests costs)	*388*	*388*	*0*	*388*	*388*
TOTAL COSTS	**539**	**519**	**131**	**408**	**388**

PN, Personalized nutrition; PP, Personalized Plan

Table 8.7.3: Polish trial: average intervention costs per participant (2020 €, (Zloty)).

Components	PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Access for participant and center (professional) + maintenance MetaDieta app/software	30 (134)	30 (134)	0	30 (134)	30 (134)
Dietician/Nutritionist appointments	112 (500)	112 (500)	112 (500)	0	0
Behavioral messages via app per participant	10 (45)	0	0	10 (45)	0
Behavioral message via app integration with MetaDieta + maintenance	10 (45)	0	0	10 (45)	0
PREVENTOMICS platform (storage data + questionnaires maintenance)	1.40 (6.23)	1.40 (6.23)	0	1.40 (6.23)	1.40 (6.23)
Extra costs grocery shopping (eating healthier)	195 (869)	195 (869)	195 (869)	0	0
Tests (blood, urine, saliva)					
Omics	154 (687)	154 (687)	0	154 (687)	154 (687)
Genetics	54 (241)	54 (241)	0	54 (241)	54 (241)
Other (e.g., overhead)	46 (206)	46 (206)	0	46 (206)	46 (206)
Total test costs	*255 (1,134)*	*255 (1,134)*	*0*	*255 (1,134)*	*255 (1,134)*
TOTAL COSTS	**612 (2,733)**	**592 (2,643)**	**307 (1.369)**	**305 (1,364)**	**285 (1,274)**

PN, Personalized nutrition; PP, Personalized Plan
* In this chapter, the intervention previously labeled as "PP+B" in both Poland and the UK (as described in Chapter 1, Chapter 5, and Chapter 9 of this PhD thesis) is now referred to as "PP". Conversely, the intervention previously known as "PP" in these countries is now labeled as "PN" in this chapter.

Table 8.7.4: UK trial: average intervention costs per participant (2020 €, (pounds)).

Components	PP*	PN*	Control	Difference PP-Control	Difference PN-Control
Access for participant and center (professional) + maintenance MetaDieta app/software	30 (27)	30 (27)	0	30 (27)	30 (27)
Dietician/Nutritionist appointments	430 (383)	430 (383)	430 (383)	0	0
Behavioral messages via app per participant	10 (8.9)	0	0	10 (8.9)	0
Behavioral message via app integration with MetaDieta + maintenance	10 (8.9)	0	0	10 (8.9)	0
PREVENTOMICS platform (storage data + questionnaires maintenance)	1.40 (1.25)	1.40 (1.25)	0	1.40 (1.25)	1.40 (1.25)
Extra costs grocery shopping (eating healthier)	376 (335)	376 (335)	376 (335)	0	0
Tests (blood, urine, saliva)					
Omics	314 (279)	314 (279)	0	314 (279)	314 (279)
Genetics	54 (48)	54 (48)	0	54 (48)	54 (48)
Other (e.g., overhead)	94 (84)	94 (84)	0	94 (84)	94 (84)
Total test costs	*462 (412)*	*462 (412)*	*0*	*462 (412)*	*462 (412)*
TOTAL COSTS	**1.319 (1,175)**	**1,299 (1,157)**	**806 (718)**	**513 (457)**	**493 (439)**

PN, Personalized nutrition; PP, Personalized Plan
* In this chapter, the intervention previously labeled as "PP+B" in both Poland and the UK (as described in Chapter 1, Chapter 5, and Chapter 9 of this PhD thesis) is now referred to as "PP". Conversely, the intervention previously known as "PP" in these countries is now labeled as "PN" in this chapter.

Appendix 8.8: Ethical issues

Details on the ethical issues considered in this health technology assessment.

This HTA addresses various ethical issues, categorized according to the HTA core model, and supported by existing literature (35,450,477). These issues were addressed to maximize benefits and minimize potential harms.

In general, the PREVENTOMICS intervention protocols (43–46) were submitted to the Ethics Committees of the centers involved in each of the studies (D7.2 ('Data management plan')). The Ethical Committees assessed the characteristics of the interventions, informed consent for each protocol, the logistics for data management within each site as well as data management

procedures that were needed for joint analysis of the information among sites. The ethical standards and guidelines of Horizon 2020 (in particular: EU Directive 95/46/EC; 2002/58/EC and 2006/24/EC) have been rigorously applied, regardless of the country in which the interventions were carried out. Furthermore, an Ethics Board comprised of representative persons from the partners involved in volunteers' recruitment and sensitive data handling, oversaw evaluating the compliance with the applicable regulations in terms of protection of rights and safety of subjects that contributed with the data used in the project.

Benefit-harm balance

When looking at the "benefit-harm balance", there were measures showing that personalized nutrition could be effective (see Table 8.3 manuscript), although the effects are not very large, with no major harms (see safety domain). Moreover, is possible that personalized nutrition could result in participants making healthier choices for other people in their lives. For example, a person who cooks for "others" (e.g., relatives) may choose to cook (healthier) foods for them as well. This might influence the eating pattern of the "others" as well. However, this would not be seen as a direct result of personalized nutrition itself. Additionally, the technology and evidence generation for assessing personalized nutrition are unlikely to have hidden or unintended consequences.

Autonomy

The intervention generally had no impact on individual autonomy, supported by different reasons. First, the PREVENTOMICS interventions was not offered to individuals that were vulnerable (and is also not aimed to be offered to vulnerable individuals when on the market), so people are always able to give informed consent. Second, all participants received an information folder before the informed consent was given and always had the right to withdraw at any time. Third, individuals that took part in these interventions were required to be more pro-active about food habits, particularly when the individual receives food recommendations. Last, since it is very common for participants to become less compliant over time, withdrawal is highly unlikely to adversely affect the doctor-patient relationship, or in the case of the pilot in the UK and Poland: the dietician-participant relationship.

Respect for persons

The use of a personalized nutrition intervention is very unlikely to have any adverse effect on human dignity or on participant integrity. One issue that will be respected is the participant's dietary preferences, which may or may not be based on religious or moral beliefs. Therefore, for example, vegetarians will never be told to eat meat. People that prefer to eat meat, can still eat meat in the Danish pilot during lunch or on their seventh day when they need to take care of their own meals.

Justice and equity

The implementation of personalized nutrition is unlikely to significantly affect the distribution of healthcare resources. The costs associated with it are generally not excessively high,

although this may vary. Furthermore, personalized nutrition interventions do not require significant reallocation of resources, as they typically involve minimal training and infrastructure requirements. However, there are factors that could prevent a group or individual from gaining access to the PREVENTOMICS interventions. One factor would be digital literacy (or really illiteracy), since the PREVENTOMICS interventions require digital skills and the use of a smartphone (e.g., for older individuals). Another related issue that could have a negative effect on the access to the interventions is the educational status. See for example D1.2 ('Consumers Report'), in which it is found that the "level of education" best explains the use of (or registration in) a health platform. People with a high level of education are more likely to use or register in these platforms (44%) than respondents with an average level of education (35%) and basic level of education (14%). In other words, PREVENTOMICS aims to be useful for everyone as a preventive tool (health and less healthy), but inequality might arise when interventions will not be reimbursed by a third party. Although people with a lower socioeconomically disadvantage appear to have poorer diets and higher disease burdens, the interventions might be more accessible to people with a greater socioeconomic advantage (446).

Legislation

Personalized nutrition is unlikely to have any impact on the realization of basic human rights or lead to any new ethical challenges at this time. Maybe In the distant future, sophisticated versions of personalized nutrition could result in dramatic health improvements, which may lead to new and unique ethical challenges (e.g., genetic testing).

Ethical consequences of the HTA

There are no obvious ethical consequences of the choices made in the pilot studies. That is, all studies used fairly standard and widely accepted endpoints and cut-off values. Moreover, no obvious ethical problems related to the data or assumptions in the economic evaluations were made. One important reason to conduct the assessment now (i.e., early HTA) is to explore the potential value of personalized nutrition based on the results of the different pilot studies. In that regard, the aim of the assessment was to support developers of personalized nutrition and not perse to support a stop-go decision for implementation/reimbursement. There is no immediate need to make decision regarding implementation at this time.

Appendix 8.9: Organizational issues

Details on the organizational issues considered in this health technology assessment.

In this HTA, there were several organizational aspects considered important for possible implementation of the PREVENTOMICS interventions, which are summarized in the text below. They were divided based on the topics suggested in the HTA core model.

Health delivery process

Overall, the PREVENTOMICS interventions could be considered supplementary on the current work of healthcare professionals (i.e., nutritionists, dieticians, or other professionals). Nutritionists are likely very familiar with the use of apps to document health behaviors, and they will also be familiar with many of the tests performed to personalize nutrition. However, the specific tests required for personalized nutrition, might not be used in current practice. A few examples of responses from partners of the PREVENTOMICS project, who are experts in this field, related to the way the PREVETNOMICS interventions might influence their current work are given below.

One response from Spain regarding the effect was the following:

"[The technology] could be considered supplementary to the way it is currently applied by nutritionists. Nutritionists usually do not ask for a genetic test nor a metabolic analysis. However, we have proved that looking at the scores gives more insights on the metabolic status than trusting the anthropometrics alone. The goal would be to move towards this type of personalization in daily practice. Also, to be used as a stand-alone service (e.g., PREVENTOMICS as a service) you might ask for a genetic test and come for the analysis or make arrangements with laboratories (equipped accordingly) where the user can go to take the samples."

A response from the UK was very similar:

"I see this as a supplement to nutritionist current practice, giving additional objective measurements that can be used to improve individual's understanding of the role of nutrition in health and the importance of making dietary change."

A response from Denmark was also quite similar:

"The technology can supplement professional dieticians' current practice in a way that uses additional biomarkers to improve individuals' health outcomes. However, this will require professionals to be knowledgeable about the technology and the use of genetics in clinical practice."

It will be important to verify whether the staff involved in providing personalized nutrition are able to perform the required tasks. Additionally, it might be important to educate and train the professionals in how to provide food recommendations, since this can lead to better results. One finding that supports this, relates to the pilots in the UK and Poland, that aimed to have similar design. However, results in the UK were more beneficial than in Poland, which could possibly be explained by the finding which is explained below:

"What I [UK researcher] found really interesting is that Controls had only standard recommendations, but for PP and PN, I got really involved when providing nutritional plans,

explaining to volunteers the scientific basis underlying the foods that had been selected for them and even challenging them when asking for the reason to choose one or another food related with their metabolic cluster. I also elaborated more developed explanations for clusters and defined specific foods to increase/decrease for the different food categories coming out from the Nutrition Recommendation Engine. This "didactic" way of providing recommendations together with extended elaboration of food recommendations was the only point that was not standardized for both pilots [UK and Poland] and might be a plausible explanation for the differences."

Overall, the PREVENTOMICS interventions did not require any new forms of co-operation and communication of activities. That is, the need to receive the lab results might require some change in co-operation. However, coordination on partners analyzing different complementary aspects on the same sample requires good communication/collaboration. In contrast, some elements of personalized nutrition might require new activities related to quality assurance. For example, it would be important to monitor whether the cluster to which a participant is assigned is the correct one, and also to monitor whether the participant was later actually assigned to the correct cluster.

On the other hand, there are the participants. The participant's flow does not change much. However, one change in flow associated with the personalized nutrition is the need for additional testing before the participant would be allocated to a cluster. Currently, participants would receive dietary advice without any prior testing. This change currently results in a delay, which may decrease enthusiasm and perhaps compliance. In contrast, participants are required to use the app to document their food habits and other information. This requires additional instruction and can also require ways to keep the participant motivated to provide the information. Additionally, an aspect not raised by the participants but worth considering is the size of the household. In households with more than one member who dine together, the practicality of preparing individualized meals for each family member should be addressed. This poses a question about the feasibility of such an approach, especially for families or larger households.

Structure of healthcare system

(De)centralization issues are unlikely to have any influence on the implementation of personalized nutrition interventions. For example, the health professionals involved in personalized nutrition (including nutritionists) can be found in every health center.

Process-related costs

The process-related costs for the PREVENTOMICS interventions are expected to be low. No new hardware would need to be purchased. Also, the software costs to provide personalized nutrition interventions are relatively low. For example, the license to use the MetaDieta app has a price of 3000 euros per year. It would probably also not influence the need for other technologies, especially not in the short term. If it results in weight loss and improved health, it could perhaps reduce the need for treatment and hospitalization.

Management

In the pilots of the PREVENTOMICS project, there were some management problems and opportunities attached to the interventions. A nutritionist from the UK reported major problems regarding the delay in receiving results needed to personalize the intervention. Specifically, there was a delay of 2-3 months from receipt of samples to receiving the results. This can result in a loss of momentum and motivation by the individual. In addition, she noted that *"the material provided needs a lot of work to be more readily usable and valuable to the dietician. Currently the onus is on the dietician to develop a lot of the supporting material and food lists, which is a loss of value added that PREVENTOMICS could otherwise capture, and which competitors could easily seize [on] to gain competitive advantage."*

However, it must be noted that there were logistical issues due to the pandemic and therefore it was not possible to analyze [samples] in one go. Moreover, some samples needed to be taken again in the UK, as they were stopped at the border because of Brexit.

A response from Spain was as follows:

"Clear logistic pathway, arrangement with laboratories. For the project we have [split] analysis into different partners, ideally, and as a service, better to minimize this or centralize as much as possible. We have observed also the need for clear instructions to volunteers in case they need to take samples themselves (e.g., saliva)."

The response from Poland was as follows:

"The nutritionists reported some minor shortcomings during the pilot, which were resolved on an ongoing basis (e.g., data flow between DSS and MetaDieta)."

A response from Denmark was as follows:

"Many of our participants were highly motivated when recruited for the study, but the design of our pilot where that all participants need to start within limited time-period. This meant that the first participants were recruited in late October, had their first visit in January and did not start up on the actually diet before mid-March. Some of the participants have later commented on this long waiting period even though they were told before they signed up for the study. Luckily, we only had 7 dropouts from when we stopped recruiting (mid Dec) to the first visits (mid Jan). Furthermore, we experienced that the platform was down half of one day, meaning that all questionnaires were filled out in hand, and were entered to the platform by staff the day after.

Moreover, other small technical issues occurred during the visit day, where a few numbers of phones could not install the apps. This was, however, solved ad hoc."

In sum, different problems have been encountered, but have already been resolved.

Culture

The PREVENTOMICS interventions were overall well accepted by the participants. One response from Spain:

"*[The system was] well accepted [by participants]. ...check this blog post prepared by OCU:* https://preventomics.eu/requirements-for-a-e-health-tool-from-consumers-point-of-view/. *This blog post describes the different principles (list of requirements) that were applied when developing the PREVENTOMICS e-health tool."*

The response from the UK was somewhat less enthusiastic:

"[Study participants] engaged well with the results presented. However, the mobile app was not easy to use and needs substantial work. It currently only allows the participant to log food intake and compare this to the dietary prescription. It did not highlight foods to include according to cluster, provide recipes, assist with creating shopping lists with alternatives more aligned to the cluster, etc. There are a lot of better apps on the market (e.g., My Fitness Pal) which are far easier to use and offer greater functionality."

However, it must be said that the objective of this pilot was not the app itself, but the software for the professionals. The app was something that can be seen as "additional".

The response from Poland highlighted both strengths and weaknesses of the system and the app:

"Most of the volunteers emphasized that the great advantage of this project is the possibility of having results not only of routine tests, but also new ones, which are currently discussed in the media, e.g., genetic risk score and intestinal microbiota tests. Regarding the use of the mobile MetaDieta app for participants, generally individuals found it to be helpful in the dietary intervention. Unfortunately, they reported that it was not possible to select certain food products to be recorded in the app. Although volunteers were given suggestions of food substitutes in the dietary plans by their nutritionists (to be used interchangeably in a meal at different weeks), they could not see these substitutes in their mobile app. So, some improvements to the functionality of the application are desired."

A response from Denmark was as follows:

"Some of the Danish participants loved to browse the SF app while other did not use it much. The app where there for inspiration so for lunches and for the day they did not received food for. The OMNI app worked more or less without any bigger issues. For the Danish study, the platform was mainly used together with staff, but many found it confusing to navigate in."

Appendix 8.10: Legal aspects

Details on the legal aspects considered in this health technology assessment.

In this HTA, several legal aspects were considered important, which are summarized in the text below. They were divided based on the topics suggested in the HTA core model. Patient autonomy was handled in a different domain (see ethical aspects above) and is not discussed here.

Privacy of the patient

Under EU standards, personal data is defined as any information related to an identified or an identifiable person (art. 4.1 General Data Protection Regulation (GDPR)) (478). Anonymized data does not fall under this definition, but the bar for "anonymized data" is set very high.

The processing of personal data (including health data and genetic data) includes (but is not limited to): collection / storage / structuring / adaptation / consultation / transmission / destruction (art. 4.2 GDPR). It is for any supplier of personalized nutrition of essence to only process personal data based on a valid legal basis, such as a consent (art. 6 GDPR). The definition of "Consent" is as follows: any freely given, specific, informed, and unambiguous indication of a data subject's agreement with the processing of his/her personal data based on a statement or clear affirmative action (art. 4.11 GDPR). The use of consent as a legal basis for the processing of personal data is further detailed in Guidelines 05/2020 by the European Data Protection Board.

If there is a valid legal basis, it remains prohibited to process health, genetic and other sensitive data unless specific conditions have been met (article 9 GDPR). This is for instance the case when the 'data subject' has given its specific consent for processing for a specific purpose (art. 9.2 (a) GDPR), or when processing is necessary for scientific purposes (art. 9.2 (j) GDPR).

In the PREVENTOMICS project, the collected data was to be stored in a secure server, only visible to the research site network (Deliverable 6.1 ('Ethical framework')). Anonymous and identifiable data was to be stored separately, and only the project authorized person(s) could have access to the stored data. Anonymity was guaranteed by separating identifiable data from anonymous data. Anonymous data was to be made available to researchers. If any identifiable data was required for the research purposes, access, and distribution to it was to be granted only after explicit permission and after agreement of the data holders (participants providing the data). Authentication was required to access stored data on the research site.

Researchers handling and processing personal and sensitive data within the project were asked to sign a statement that they were familiar with and abided by the contractual obligations of the consortium. If not included in this obligation, they had to sign a statement that committed them to ensure project data were not provided to persons outside the project consortium.

Equality in healthcare

There is a variety of laws and binding rules that guarantee equal access to technologies, in which there are also cross-country differences. One example of a European wide right, that ensures equal access, is the non-discrimination right (479). This law prohibits discrimination based on factors such as race, sex, age, disability, or socioeconomic status. By means of this law, everyone should have an equal opportunity to access and benefit from personalized nutrition regardless of their personal characteristics or circumstances. Another example is the general food law (480), that states that European citizens need to have access to safe and wholesome food of highest standards.

However, there are cross-country differences in rules and regulations regarding equality in healthcare. For example, as mentioned before in Appendix 8.6 and domain 'description and technical characteristics of the technology', there are cross-country differences in reimbursement and insurance coverage. Some countries have health insurance systems that cover digital health or specific medical services, including nutritional counseling or consultations, while others have not. The availability and extent of insurance coverage for personalized nutrition services can significantly impact accessibility, as those without coverage may face financial barriers to accessing such services (see also 'ethical' domain).

Ethical challenges of existing legislations

Testing involved in personalizing nutrition looks like tests that are currently available and it is therefore unlikely that use of the technology will lead to ethical challenges that have never been considered before and not addressed in existing legislation. However, one of the main objectives of current legislation is privacy and data protection. The kinds of analyses in PREVENTOMICS, mainly genetics, but also metabolomics, could provide large volumes of information about the user that might put anonymization at risk. Therefore, care must be taken when this data is used and shared with others. Moreover, it must be noted that personalized nutrition is a multifaced phenomenon, so many different rules and regulations need to be combined, in which blurred boundaries exist between "health" and "lifestyle" products and "food" or "medicine" (452).

Authorization and safety

The MetaDieta app/software should be considered as a "medical device". A medical device is any device, software or other article intended by the manufacturer to be used for specific medical purposes (e.g., prevention of a disease) (478). Therefore, the Medical Devices Regulation (MDR) is applicable in which a CE mark was needed (481).

Ownership and liability

Deliverable 7.5 ('Final plan for the Use and Dissemination of Results-PUDR') provides information on the dissemination and exploitable results of the PREVENTOMICS project, including ownership rights and intended IPR protection strategies, as well as a summary of dissemination actions and future activities. In brief, two different approaches were suggested,

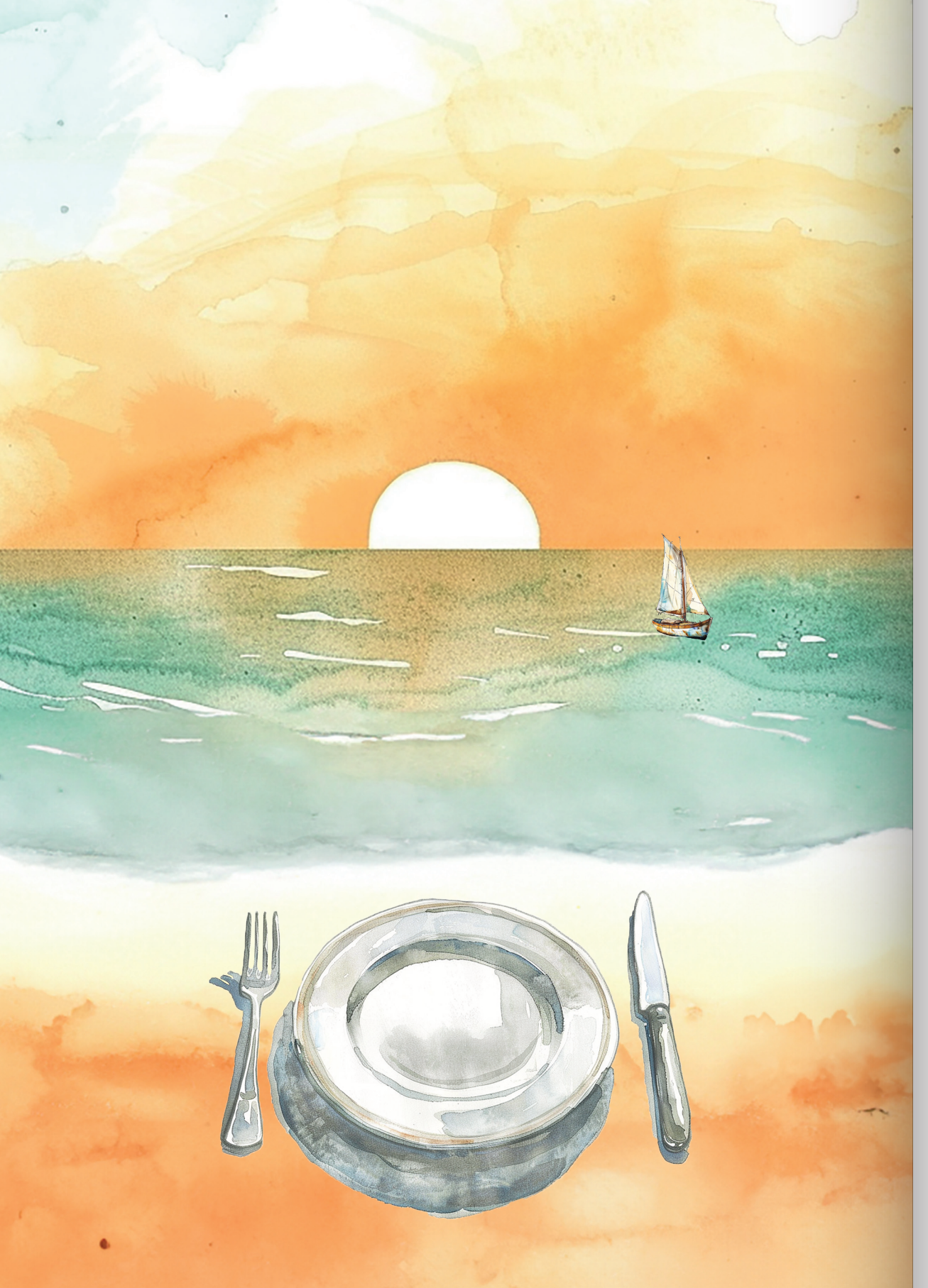
which allow for flexibility of choice among partners. This is necessary since this is a complex project and the management of multiple relationships between partners and a new approach was set up within the Joint Exploitation Routes. These approaches are: Joint Venture and Licensed results.

First, regarding a joint venture approach, the vision will be to create a separate company or legal entity where ownership is distributed based on partners' allocated efforts and contribution to each of the project developments. The Joint Venture will have its own structure: its shareholders are expected to be the core partners of the project plus any external 3rd party company that provided added value and wishes to join the venture. The Joint Venture will have its own team of dedicated professionals, such as technicians, managers, engineers and commercial agents. An IP Entity Manager can be appointed to deal with business development matters as well as neutral administrative work.

The second approach is a licensed results approach, which is based on licensing the results of the project into separate entities that will deal with the commercialization of the PREVENTOMICS platform. This way, there are no direct legal relationships amongst the project partners, which can facilitate and speed the go-to-market strategy of the technologies, as there are no complicated negotiations. Two options in this approach are available for exploration: IP Brokering and IP Transfer. Both of these are set on the philosophy that the project results are licensed to an intermediary, which will receive a percentage fee for the commercialization efforts and can include the PREVENTOMICS Platform in their own portfolio of services/products and their business model.

Regulation of the market

In the case of personalized nutrition, it is unlikely that there are any relevant price control mechanisms. However, further assessment is needed to verify this. Moreover, it is unlikely that there are any legal restrictions to marketing the personalized nutrition. This is partly because the target population does not include persons with serious diseases and also because the forms of personalized nutrition developed in PREVENTOMICS do not involve any important health risks. It is however important for developers of any personalized nutrition intervention to consider whether or not their product will be seen as a medical device. This is not easy to determine since it remains the question when a device will transform from a lifestyle product to a medical device. For example, an app with diet recommendations based on potential health data can be seen as a lifestyle product. However, when its developers claim that the app can help to address or threat a medical condition like obesity, it transforms into a medical device. Additionally, developers of personalized nutrition interventions also need to be aware that the food market is highly regulated by the European Food Safety Authority (EFSA) (see Deliverable 7.4 ('PUDR')) (452).



Chapter 9

General discussion

The global burden of various diet-related diseases, such as ischemic heart disease (IHD), stroke, and diabetes, underscores the importance of proactive measures to prevent these diseases (1). Diets play a crucial role in preventing such diseases and can also contribute to the prevention or management of associated issues like obesity and high blood pressure (4–7). Acknowledging the limitations of population-based approaches in addressing dietary challenges, there is a growing recognition of the different individual responses to nutrition (11,21,23). This emphasizes the importance of the innovative personalized nutrition approach.

By addressing challenges in this field, the PREVENTOMICS project emerges as a pioneering initiative that harnesses advanced technologies, including omics, to offer personalized nutrition advice (41). This PhD thesis investigated the potential of personalized nutrition interventions, using the PREVENTOMICS interventions as practical examples, through an early Health Technology Assessment (HTA). The overarching goal was to provide insights that would assist diverse stakeholders in healthcare decision-making. These insights relate to the development and implementation of personalized nutrition interventions into the market to mitigate diet-related diseases.

The investigation included an examination of the potential cost-effectiveness of personalized nutrition interventions, specifically the interventions developed and tested during the PREVENTOMICS project. Additionally, the preferences and willingness to pay (WTP) of the general population concerning personalized nutrition interventions were studied. Furthermore, the study explored other crucial HTA aspects that should be considered for the development and implementation of personalized nutrition interventions.

This general discussion unfolds with comprehensive answers to the research questions, followed by a deeper exploration of the implications of the research findings. These insights are tailored to assist developers, policymakers, and users in navigating the intricate landscape of personalized nutrition interventions. The discussion concludes with an examination of future research areas (including recommendations for HTA researchers), and some final reflections. This includes the question of whether personalized nutrition interventions should be genuinely regarded as a 'hope' or merely a 'hype.'

MAIN FINDINGS

What is the potential cost-effectiveness of personalized nutrition interventions, including the PREVENTOMICS interventions studied in different countries?

Parts I (preparation) and II (competitions) of this thesis were entirely dedicated to addressing this crucial question, emphasizing the importance of evaluating the cost-effectiveness of personalized nutrition interventions. This significance lies in the potential improvement of health outcomes and the introduction of additional costs because of advanced technologies (e.g., omics analyses) (47,48). **Chapter 2** presents results from a comprehensive and systematic

literature review of the current state of knowledge regarding the cost-effectiveness of interventions incorporating personalized nutrition elements in adults. From the 1792 unique records, 49 papers were selected for the review. Notably, significant variation was observed in the methodologies employed across the studies, encompassing differences in time horizons, comparators, modeling assumptions, and the intervention approach.

In **Chapter 2**, we also identified a notable diversity in study populations, with most studies focusing on individuals with obesity, diabetes, or exhibited impaired glucose tolerance (IGT) (28 studies). This emphasis is likely due to the significant impact of these conditions on diet-related diseases (9,10). While these diseases are not exclusively prevalent in individuals with these conditions, these conditions hold particular significance.

Chapter 3 assessed the lifetime health and economic burden of obesity across five European countries, employing a newly developed health economic model. The study also evaluates the potential impact of prevention. Results show that a one-unit reduction in BMI due to a preventive intervention (e.g., personalized nutrition) would result in a longer life expectancy and more quality-adjusted life years (QALYs). This effect was higher for people with a BMI of 35 kg/m^2 compared to people with a BMI of 30 kg/m^2. The associated savings in medical costs for diabetes, IHD, and stroke were lowest in Greece and highest in Germany. Notably, in the Netherlands, there was an overall increase in total costs, primarily driven by increases in medical costs for other diseases (i.e., unrelated medical costs). In summary of **Chapter 3**, decreasing BMI yields health gains (especially in higher BMI ranges), reductions in obesity-related healthcare costs, but an increase in non-obesity-related healthcare costs. This underscores the importance of considering all costs in decision-making regarding the implementation of preventive interventions.

Hence, all costs were included in our (base-case) cost-effectiveness analyses in **Chapters 4-6**, where we assessed the cost-effectiveness of the PREVENTOMICS interventions using the model described in **Chapter 3**. The model underwent customization for each country, aligning with data from the PREVENTOMICS trials. Incremental costs and QALYs of all chapters, plus additional analyses explained later in this discussion (subsection 'Choice of comparator'), are presented in Figure 9.1.

Chapter 4 specifically investigated the cost-effectiveness of a personalized nutrition plan (PP), entailing the delivery of personalized, easy-to-prepare meal boxes, compared to a general nutrition plan (non-personalized meals (control)). The trial in Denmark revealed incremental costs of 1,749 euros, primarily attributed to the labor intensity of preparing unique meal boxes. Importantly, the overall incremental costs over a lifetime were therefore high, coupled with small incremental QALYs, rendering the intervention not cost-effective (incremental cost-effectiveness ratio (ICUR): €158,798 per QALY). However, it is crucial to note that this does not mean that this intervention has no possibility of being cost-effective. Scaling up the intervention could significantly reduce per-patient costs, potentially rendering the

intervention cost-effective. For example, a 20% decrease in intervention costs would reduce the ICUR to €23,668 per QALY gained.

In **Chapter 5**, the results showed that the incremental (intervention) costs of personalized nutrition plans involving dietary recommendations by a dietician (with or without a behavioral change program (PP+B and PP)) compared with a control (non-personalized plan) were notably lower than those in Denmark. The trials described in this chapter were conducted in the United Kingdom (UK) and Poland. Lifetime analyses revealed that PP+B and PP could potentially be cost-effective compared to the control in the UK (ICUR PP+B: €14,607 (£13,006) per QALY, PP: €13,726 (£12,222) per QALY). In Poland, results from the lifetime analyses showed that PP+B may be cost-effective compared with the control, with an ICUR of €22,915 (102,018 PLN) per QALY. Conversely, when PP was compared with the control, the intervention was dominated by the control, indicating higher lifetime costs and lower QALYs for PP. Subgroup analyses revealed cost-effective estimates for males across all interventions in all countries. Notably, considerable uncertainty surrounded the effectiveness of the trials, and sensitivity analyses suggested potential (improved) cost-effectiveness outcomes by utilizing the confidence intervals (CIs) of trial effectiveness.

In **Chapter 6**, the trial results of two personalized nutrition plans entailing recommendations for food products (with or without a behavioral change program (PP and PN)) were also compared with a control (non-personalized plan). This trial was conducted in Spain. The (lifetime) base-case analysis indicated that PP and PN were not cost-effective when compared with the control (ICUR PP: €172,789, PN: €50,108). This was primarily because of the minimal QALY gain over a lifetime. However, when focusing on subgroups of individuals with obesity, the interventions yielded cost-effective outcomes (ICUR PP: €21,501, PN: €9,955). This finding aligns with findings from **Chapter 3**, where higher BMI correlated with more QALY gain.

In summary, while the incremental effects of personalized nutrition tend to be minimal, the additional costs associated with these interventions are overall also minimal (see Figure 9.1). This aligns with expectations and serves as a classic example of a preventive measure (482), particularly in the context of personalized nutrition (see **Chapter 2**). Variations in cost-effectiveness outcomes exist among the PREVENTOMICS interventions (**Chapter 4-6**), which aligns with the variation found in the systematic review done in **Chapter 2**. If we use the language of 'sport competitions', we could say that overall, the PREVENTOMICS intervention that integrated a platform into a software for nutrition professionals in the UK "wins" in terms of cost-effectiveness (**Chapter 5**). The integration of the platform in an app for a catering company in Denmark "loses" (**Chapter 4**). The differences in cost-effectiveness results in the different chapters could be attributed to various factors such as the interventions themselves, the countries in which the trials were conducted, the study populations, and uncertainties surrounding costs and effects. More efforts are needed to enhance certainty around conclusions regarding the cost-effectiveness of personalized nutrition. These efforts

will be discussed in the sections 'Implications and recommendations for stakeholders' and 'Future research'.

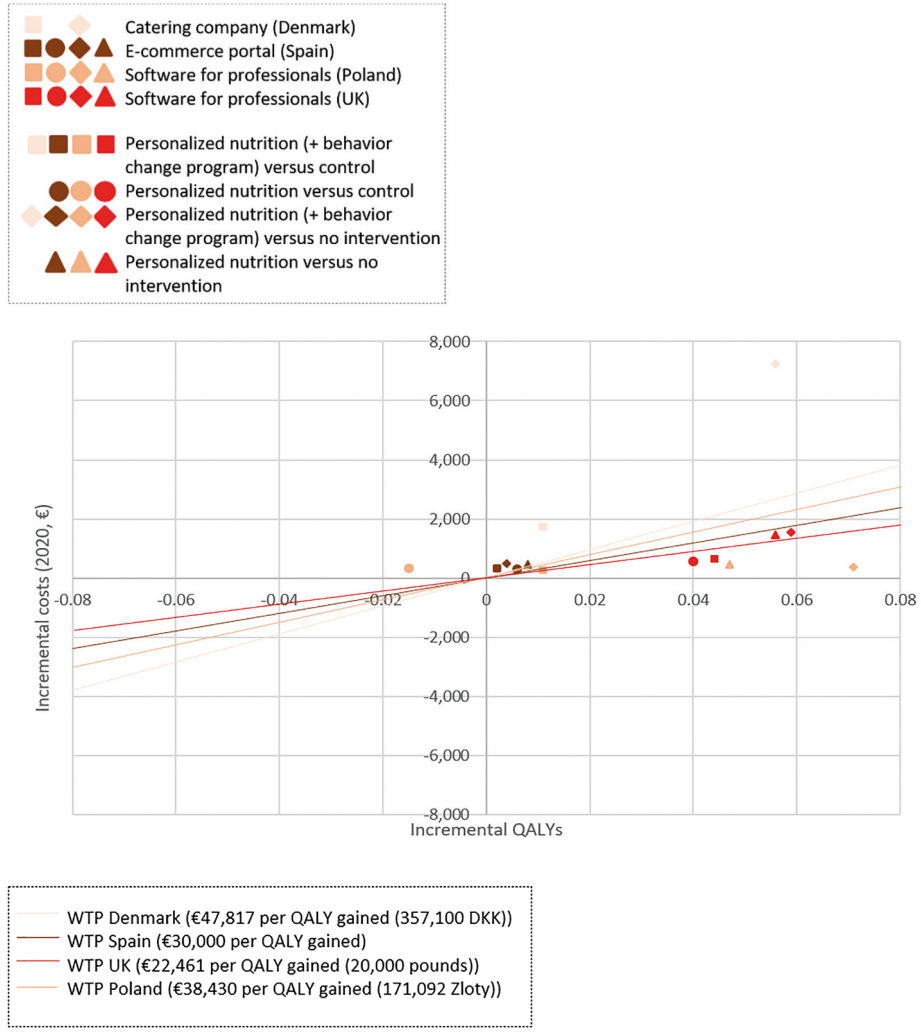


Figure 9.1: Cost-effectiveness plane: comparing results of personalized nutrition interventions versus a control intervention or no intervention. DKK, Danish Krone; QALY, Quality-adjusted life year; UK, United Kingdom; WTP, willingness to pay.

What are the preferences and WTP of the general population regarding personalized nutrition interventions?

As emphasized in the introduction, preference data is increasingly recognized as valuable (additional) evidence for healthcare decision-making (55–57). Therefore, we examined the preferences of the general population for personalized nutrition interventions in **Chapter 7**. With this, we made the transition from cost-effectiveness analyses to a broader approach

(Part III (transition)). In this chapter, we conducted discrete choice experiments (DCEs) in five countries, each with 500 respondents. The data from these DCEs were analyzed with panel mixed multinomial logit models to assess preferences.

Results revealed that, across all countries, the total expenditure on nutrition was the primary factor influencing the preferences for personalized nutrition interventions. Participation rates for specific hypothetical scenarios varied but were generally high, reaching a maximum of 81% for 'personalized nutrition advice' and 87% for 'personalized meals' in Spain. Rates for scenarios that were somehow similar to the PREVENTOMICS interventions ranged from 26% to 49% across countries and interventions. The highest WTP estimates were associated with achieving six kilograms of weight loss (the maximum value studied). For example, Polish respondents were willing to spend an extra €25.78 per week for 'personalized meals' to lose 6 six kilograms over a 4-month period.

While differences in preferences both between and within different countries were observed, the overall results from **Chapter 7** indicated a WTP for and willingness to use personalized nutrition interventions. Nevertheless, the findings underscore a need to address the pricing structure of personalized nutrition interventions, including the PREVENTOMICS interventions. The current costs associated with PREVENTOMICS across various use cases exceed the amounts respondents are willing to pay.

To illustrate, the highest observed WTP within the interquartile range (IQR) for personalized meals was €59.45 per week (= €594.50 for 10 weeks). This is considerably lower than the €7,402 cost for ten weeks of the comparable PREVENTOMICS catering intervention (see **Chapter 4**). Fortunately, the costs of the other two PREVENTOMICS interventions (focusing on personalized advice) studied in **Chapter 5 and 6** were lower than the costs of the catering intervention. These costs range from €519 for the e-commerce intervention in Spain to €1,319 for the software for professionals in the UK. The maximum WTP observed in our DCE for this type of intervention (i.e., personalized advice) within the IQR is €42.12 per week. This is equivalent to €732.57 over four months. Theoretically, this amount remains above the intervention costs of Poland and Spain. However, it is crucial to note that this WTP is contingent on losing six kilograms in weight compared to no weight loss. This benchmark may not be presently achievable for PREVENTOMICS interventions.

In conclusion, the study revealed that pricing is the decisive factor influencing individuals' use of personalized nutrition interventions and thereby adds a significant value to healthcare decision-making. If the costs are higher than the WTP of individuals, which is the case for the PREVENTOMICS interventions, there is a need to address out-of-pocket expenses for potential users. What this means for different stakeholders will be discussed in the next section 'Implications and recommendations for stakeholders'.

Beyond cost-effectiveness and preferences, what other crucial health technology assessment (HTA) aspects should be considered for the development and implementation of personalized nutrition interventions?

While (cost-)effectiveness usually forms the primary focus in HTA, and preferences are gaining increasing attention, **Chapter 8** underscores the importance of also considering other crucial aspects. It accentuates various factors vital for (re)consideration, aligning with different domains within the HTA core model. The diverse aspects identified for the development and implementation of personalized nutrition interventions, as outlined in **Chapter 8**, are summarized in Table 9.1. The implications and recommendations for diverse stakeholders, related to these different aspects, will be discussed in the next section 'Implications and recommendations for stakeholders'.

Table 9.1: Aspects that should be considered in an HTA of personalized nutrition interventions, including implications for developers, policymakers, users and recommendations for future research.*

HTA core model domain	Key aspects to be considered	Implications for developer	Implications for policymaker	Implications for users	Future research recommendations
Health problem and current use of technology	• Huge health and economic burden related to overweight and obesity. • Limited success of current policies to tackle overweight and obesity in adults (and children).	• Investigating the potential for expanding the scope to a more 'family-oriented approach,' encompassing children, through the incorporation of supplementary features.	• Considering subgroup reimbursement (e.g., individuals with obesity and interventions that involve health professionals). • Contemplating a broadened focus on treatment/management rather than solely emphasizing 'prevention'. • Shift focus from 'lifestyle' interventions alone and consider a broader spectrum of socio-economic status (SES)-related and unrelated factors. • See 'description and technical characteristics of technology'.	-	• Consider studying additional study populations (e.g., athletes).
Description and technical characteristics of technology	• The PREVENTOMICS interventions offer a unique approach. • Reimbursement policies for these types of interventions vary across and within countries. • Typically, not reimbursed, but recent initiatives suggest that reimbursement of PREVENTOMICS interventions is possible.	• Use 'lay language' in explaining the intervention characteristics, benefits, and risks. • Incorporate features that address all lifestyle elements, such as the addition of physical activity components. • See 'organizational aspects'.	• Contemplate the promotion of interventions that incorporate both nutrition and physical activity aspects. Moreover, consider a gender-specific approach in the primary focus. • See 'health problem and current use of technology' and 'costs and economic evaluation' regarding reimbursement.	• See 'organizational aspects'.	-

Table 9.1: Continued.

HTA core model domain	Key aspects to be considered	Implications for developer	Implications for policymaker	Implications for users	Future research recommendations
Safety	• PREVENTOMICS interventions are generally safe. • Minor issues relate to drawing blood, needle management and the possibility of receiving the wrong intervention.	• See 'description and technical characteristics of technology', 'ethical aspects', and 'legal aspects'.	• See 'legal aspects'.	-	• See 'clinical effectiveness' and 'costs and economic evaluation'.
Clinical effectiveness	• Small, but overall positive (both significant and insignificant) effectiveness results were observed from the PREVENTOMICS trials. • Differences in long-term health outcomes (i.e., incremental QALYs) between interventions and control were overall (slightly) positive.	• Assist in conducting new trials.	• Support additional research, including the support of 'larger' and 'longer' trials.	-	• Consider (additional) comparators, including methodologies for evidence generation (i.e., new trials or indirect comparisons). • Prioritize large-scale trials with extended follow-ups, accounting for some implications. • Consider other (additional) clinical outcome measures and quality of life measures. • Close collaboration between clinical researchers and HTA researchers in early stages of development to keep track of the rapid discovery of biomarkers.

Table 9.1: Continued.

HTA core model domain	Key aspects to be considered	Implications for developer	Implications for policymaker	Implications for users	Future research recommendations
Costs and economic evaluation	• Interventions had higher costs compared to the control over trial periods. • Over lifetime, lower costs related to diabetes, IHD and stroke were (partly) offset by higher costs in other areas (i.e., unrelated medical costs, non-medical costs, and informal care). • Some interventions were deemed cost-effective. • Personalized nutrition interventions would (potentially) have a substantial budget impact.	• Consider an appropriate price, including discussions with policymakers about pricing and reimbursement options and scaling-up interventions to reduce prices.	• Consider different pricing and reimbursement strategies, including subgroup reimbursement, co-payments, value-based and performance-based pricing, and financial incentives.	-	• Expanding HTA with MCDA. • Add additional value elements in economic evaluations (e.g., personal utility, environmental spillovers). • Pay specific attention to the adjustment of testing costs for specific settings. • Include uncertainty around evidence generated by expert judgment. • Consider the use of other (than standard) discount rates. • Consider the use of patient-level modeling. • An ongoing collaboration to enhance the HTA Core model for personalized nutrition interventions. • Conducting economic evaluations with additional (or refined) study populations. • Conduct VOI analyses. • See 'clinical effectiveness'.
Ethical aspects	• Favorable benefit-harm balance. • Health inequality may rise when interventions need to be paid out-of-pocket. • Challenges for elderly in using digital interventions.	• Enhancing communication about benefits and risks (e.g., offering additional online or telephone support). • See 'description and technical characteristics of technology'.	• By considering different pricing and reimbursement strategies (see 'costs and economic evaluation), health inequalities may decrease. • Re-consider the definition of obesity as a disease (which results in medicalization). • See 'health problem and current use of technology'.	• Finding the right balance between prevention versus medical treatment.	-

Table 9.1: Continued.

HTA core model domain	Key aspects to be considered	Implications for developer	Implications for policymaker	Implications for users	Future research recommendations
Organizational aspects	• Overall considered supplementary to existing work processes for professionals. • Some difficulties in using the apps, but all seem to be resolvable.	• Adding features related to societal context (e.g., for dining out and multimember-households (see also 'health problem and current use of technology'). • (Keep) providing ongoing support for the technology. • Raise awareness of emerging biotechnologies by healthcare professionals.	• Consider country-specific and health service-oriented pricing and reimbursement strategies. • Raise awareness of emerging biotechnologies by healthcare professionals. • Support trainings for increasing self-efficacy among healthcare professionals.	• Attend trainings to increase self-efficacy.	-
Patients and Social aspects	• Diet satisfaction slightly increases in all intervention groups. • Willingness to use and pay for personalized nutrition interventions. • Differences in likelihood of undergoing genetic testing was found in literature.	• See 'description and technical characteristics of technology', 'ethical aspects', and 'legal aspects'.	• See 'health problem and current use of technology'.	• Ongoing partnership between patient and clinician (to align with individual needs and preferences).	• Investigating patient preferences with latent class modeling (with DCE data).

Table 9.1: Continued.

HTA core model domain	Key aspects to be considered	Implications for developer	Implications for policymaker	Implications for users	Future research recommendations
Legal aspects	• Lack of specific legal regulations for personalized nutrition. • Some, however, apply to all personalized nutrition interventions. including, GDPR and CE marking for medical devices.	• Improve the benefit-risk balance feelings by pushing policymakers to develop a cohesive legal framework.	• Develop a cohesive legal framework for personalized nutrition interventions.	-	-

DCE, Discrete Choice Experiment; GDPR, General Data Protection Regulation; HTA, health technology assessment; IHD, ischemic heart disease; MCDA, multiple criteria decision analysis; QALY, quality-adjusted life year; VOI, Value of information.
*Several implications and recommendations span across multiple HTA Core model domains. While documented under one specific domain, they are cross-referenced in another domain for a more comprehensive and integrated understanding.

IMPLICATIONS AND RECOMMENDATIONS FOR STAKEHOLDERS

The comprehensive findings of this thesis have far-reaching implications and recommendations for various stakeholders involved in the context of personalized nutrition interventions. The discussion below outlines key considerations for developers, policymakers, and users of personalized nutrition, which are also summarized per (HTA core model-) domain in Table 9.1 of this discussion. This will be done to address our last set aim for this thesis whether personalized nutrition is merely a hype or real hope. Within this section we stay in the transition phase (part III) of the Matveyev model (79); we reflect on the findings and decide what is best to consider for development, implementation, and future research (i.e., for the next cycle (preparation phase)).

Developer

As this thesis focused on an early HTA, it consequently aimed to support developers (i.e., service providers) of personalized nutrition by providing insights into the design and management of technologies (52,54). While earlier chapters highlighted specific technological aspects, this subsection investigates critical issues in more detail and addresses overarching concerns.

Daily life practicalities

Before introducing personalized nutrition interventions to the market, particularly the PREVENTOMICS interventions, it is crucial to address key considerations related to the practical aspects of daily life. Although **Chapter 8** touched upon some of these issues, not all of them received sufficient attention. The 'organizational aspects' domain in this chapter primarily focused on professional- and trial-related matters. However, it is crucial to extend the examination beyond these aspects, recognizing that PREVENTOMICS interventions require adjustments for seamless integration into daily life. This involves considering various elements of individuals' social context, which can significantly impact behavioral change and thereby also the effectiveness of the interventions (422,483–485).

The first concern for the developer of PREVENTOMICS interventions, in tackling social context-related issues, is to address the constraints individuals encounter while dining outside their home (484). While the acceptance of personalized nutrition is higher at home (483), many people regularly dine out. Developers should therefore concentrate on adapting personalized nutrition intervention technologies for situations outside the home. More specifically, this could be done through apps that can provide personalized advice for dining out. For example, integrating GPS technology and additional algorithms can link location-based services to the PREVENTOMICS platform, offering personalized recommendations for specific restaurants. This goes beyond linking supermarkets, as demonstrated in the E-commerce PREVENTOMICS intervention studied in Spain. Another approach involves incorporating a 'scan' option into the PREVENTOIMCS application to analyze restaurant menus, providing personalized recommendations based on an underlying algorithm. These approaches enable individuals to (easily) utilize personalized nutrition interventions while dining outside their home.

The second crucial aspect regarding social context involves the consideration of a household with multiple members (484). Addressing the practicalities of 'personalizing' food for a multi-member household in daily life presents challenges. Preparing individual meals for each household member based on diverse personalized food recommendations may not be practical. A proposed upgrade for PREVENTOMICS interventions includes a feature to connect and consolidate personalized data (and recommendations) for each household member. More specifically, users sign in multiple household members to the same account, enabling joint 'personalized' nutrition recommendations through an algorithm that identifies similarities among personalized data (and recommendations). It is important to note that this is an additional function and would allow household members to still follow their 'own (not similar)' personalized recommendations when dining separately, such as during lunch breaks at work. This added functionality facilitates the integration of interventions into daily life.

By incorporating this additional 'multi-member household' feature, the PREVENTOMICS interventions transition from being solely focused on adults to adopting a more family-oriented approach that includes children. This technological enhancement is crucial, given the well-documented health consequences of poor nutrition in children (11). While the prevalence of obesity is lower in children compared to adults, the associated social inequalities and health impacts are significant (11). Despite incurring some additional development costs to make PREVENTOMICS interventions family-oriented, the expanded target group is likely to enhance overall effectiveness. The integration of these features within the same applications may mitigate substantial increases in intervention costs, potentially leading to improved cost-effectiveness. However, additional confirmation through cost-effectiveness analyses is necessary.

Thirdly, ongoing support from the personalized nutrition service provider is essential, along with the opportunity for users to connect with others undergoing a similar program (484). The current PREVENTOMICS interventions already provide a continuous support option, which means that no further action by the developer is required in this regard. However, it is crucial for the developer to ensure the maintenance of this support as the intervention is introduced to the market. Furthermore, developers could enhance user interaction by incorporating a chat environment within the applications, representing a relatively minor adjustment.

Benefit-risk balance feelings

In **Chapter 7,** various intervention-related characteristics were considered as attributes in the DCEs, in which a factor important for consumer acceptance ('privacy risk') was not included (422,483). There were two reasons for excluding 'privacy risk' as an attribute. The first reason relates to the fact that minimal or no privacy risks within the PREVENTOMICS interventions were expected. The second reason is that we viewed privacy more as a broader technological factor critical for the successful implementation of personalized nutrition interventions in

the market. It was therefore considered as a background factor rather than an intervention-specific characteristic to be included as an attribute.

However, research thus indicated that consumers' perception of the benefit-risk balance (e.g., health gain versus privacy risks) significantly influences their acceptance of personalized nutrition (422,483). Consumers express concerns about privacy, particularly in sharing DNA information (486). These concerns might exceed the perceived benefits of personalized nutrition, resulting in an unfavorable balance of benefit-risk feelings. Consequently, developers need to tackle privacy concerns thoroughly (486). One way of doing so is to assure that the interventions meet all legal requirements. As stated in **Chapter 8**, this includes the General Data Protection Regulation (GDPR) for personalized data and the requirement of CE marking for medical device regulation in the European market (451). However, as also stressed in this chapter, it is important that developers also push policymakers to develop a cohesive legal framework (450,452), in which developers of personalized nutrition could follow specific legal regulations. If a clear regulation exists, which could guarantee for example consumers against potential misuse of information, the balance of benefit-risk feelings might get more favorable (450,486).

Equally important to addressing the actual privacy risks and clear regulations is effective communication about both benefits and risks. Developers should enhance consumer perception of information control, privacy risks and service effectiveness, assuring them of the competency and reliability of the technologies. As blood sampling methods, which are needed for information about DNA, become more commonplace with advancements in medical technologies, some concerns may naturally diminish (487). Nevertheless, enhancing communication, such as offering additional online or telephone support, could further ease current concerns related to data sampling (487).

Moreover, it is crucial for developers to employ 'lay language' to explain all facets of personalized nutrition interventions, encompassing privacy risks and effectiveness, as part of enhancing communication. This is particularly important as poor health literacy is a significant challenge globally (488). A population survey conducted by HLS19 Consortium of the WHO Action Network M-POHL (2021) revealed, for example, a range of people with 'limited' health literacy between 25%–72% in Europe (489). Plain language, devoid of complex medical terms and jargon, along with explanations and examples, improves comprehension (488) and thereby adherence (490). Developers could use freely available readability assessment tools (e.g., the Automatic Readability Index (491)) to ensure that the provided information is understandable. In this way, developers could play a role in reducing health inequalities, by ensuring that personalized nutrition interventions are accessible to people with all different levels of health literacy.

Cost considerations

The final consideration for developers centers on the intervention costs of personalized nutrition. In essence, what is the appropriate pricing for these interventions? A focus group-based study showed that respondents link price to the quality of personalized nutrition services (487). If the price is too low, they perceive the intervention as inferior. Paying for personalized nutrition is linked to achieving desired benefits, ensuring data protection, and qualified individuals at the service end. Moreover, payment symbolizes validation and a contractual, legal right to redress (487). Additionally, paying signifies commitment; respondents in another study expressed higher compliance when paying for the service (484). Together with our findings in **Chapter 7**, this suggests that people are willing to pay for personalized nutrition interventions. Developers may therefore consider charging users, but may face challenges in setting an appropriate price. **Chapter 7** underscores the significance of 'price' as a crucial factor influencing preferences for personalized nutrition interventions. Since the WTPs were generally lower than the costs associated with PREVENTOMICS interventions (discussed in the 'Main Findings' section), evaluating pricing demands careful consideration. Developers should discuss pricing and reimbursment strategies with policymakers; this is elaborated further in the 'Pricing and reimbursement strategies of personalized nutrition' subsection. However, if users must bear the costs themselves (i.e., no reimbursment by third parties possible), developers should actively pursue cost reduction strategies for enhanced accessibility. Scaling-up interventions, as discussed in **Chapter 3**, might be a feasible approach to reduce costs (and thereby the price) of interventions.

Policymaker

An early HTA can inform a broader range of stakeholders beyond developers alone. Recognizing the potential value of emerging products during the development stage, a key aspect of the 'early' HTA definition established by IJzerman et al. (54) (as outlined in the introduction), is also crucial knowledge for policymakers (e.g., for regulatory and reimbursement strategies (52)). Consequently, the implications derived from the findings of this thesis extend to policymakers and are addressed in this subsection. While many considerations necessitate collaboration between policymakers, payers and developers, the main responsibility of the implications outlined in this subsection rests with the policymaker.

Pricing and reimbursement strategies of personalized nutrition

Effectiveness studies highlight personalized nutrition's potential to improve health outcomes (despite existing uncertainties) (24,36,47,369,370,391). Because of this potential, it might be good to consider implementation options for these interventions. This includes the consideration of pricing and reimbursement strategies, varying from full coverage to fully out-of-pocket expenses. The costs of personalized nutrition may exceed consumer financial capacity, necessitating some form of third-party coverage (i.e., coverage from health insurance or government agencies). In the drugs market, patient access and reimbursement decisions are grounded in HTA, with certain countries incorporating the ICUR into their evaluations (492). The ICURs calculated for new drugs are compared with a predefined value-for-money criterion,

typically denoted as the WTP threshold. Although this approach was applied in **Chapters 4-6,** showing that some personalized nutrition interventions are potentially cost-effectiveness for the entire population or specific subgroups, this is currently not applied in practice (321). The landscape for personalized nutrition interventions lacks a systematic framework for final decisions regarding the determination about what merits reimbursement. Policymakers are therefore presented below with a diverse range of potential pricing and reimbursement strategies for personalized nutrition interventions.

Subgroup reimbursement

The current user demographic of personalized nutrition predominantly comprises a small percentage of motivated consumers, often of higher socioeconomic status (SES) (372). Conversely, individuals with lower SES in developed countries often exhibit poorer dietary habits, higher BMI, and increased disease burdens (11,446,493). **Chapter 6** showed better (cost-)effectiveness results of personalized nutrition interventions in individuals with obesity compared to the general population. In turn, this implies that those with a higher BMI (and probably individuals with lower SES) could potentially derive the most significant benefits from personalized nutrition. Paradoxically, these individuals, who stand to gain the most, may face financial constraints that limit their ability (and willingness) to invest in diet-related interventions (178,420). This dynamic introduces a concerning prospect of increased health inequalities: those who need personalized nutrition the most might struggle to afford it, while those with less urgent needs may find it more accessible. Reimbursing personalized nutrition interventions by a third-party payer might be a solution for making the interventions accessible for all individuals.

Recognizing the budgetary constraints faced by healthcare decision-makers, it is advisable to adopt a strategic approach when considering reimbursement for interventions. One option is to reimburse effective personalized nutrition interventions exclusively to subpopulations experiencing the highest health- or economic burdens. This could be those individuals with obesity, potentially targeting individuals with lower SES (254). Embracing this targeted strategy not only enhances accessibility to personalized nutrition interventions but also holds the promise of reducing health inequalities. This approach, coupled with the potentially improved (cost-)effectiveness for populations with obesity (and likely lower SES) as discussed in **Chapter 6**, allows policymakers to avoid a trade-off between efficiency and equity (494).

Another insight emphasizing the importance of (subgroup) reimbursement for individuals with obesity stems from the findings in **Chapter 7**. Specifically, individuals who currently spend less on nutrition, possibly indicative of a more affordable yet less healthy dietary pattern (376), generally express lower WTP. It is reasonable to deduce that this group likely comprises individuals with obesity (and consequently individuals with lower SES), given that poor nutrition can contribute to obesity (11). This reinforces the notion of reimbursing personalized nutrition interventions for obesity populations to enhance their uptake. However, it is crucial to note that **Chapter 7** did not explicitly investigate the composition of the 'lower current

expenditure' group. The underlying reasons for this observation (i.e., lower expressed WTP) remain therefore ambiguous based on the information presented in **Chapter 7**. Other potential contributing factors to this finding, aside from lower SES, may involve a diminished perception of the importance of nutrition, reduced motivation to adopt healthy eating habits, or numerous other unidentified factors (see also subsection 'Consideration of a holistic approach') (495).

Policymakers may want to explore the option of limiting reimbursement not only to individuals with obesity but also exclusively to personalized nutrition interventions involving a health professional. This consideration arises from the observed higher likelihood of adherence to a nutrition intervention when a health professional is involved, compared to individuals using personalized nutrition interventions independently (487,496–498). Health professionals, such as dietitians or nutritionists, can offer valuable insights, motivation, and a structured plan, thereby enhancing adherence. In contrast, individuals opting for independent nutrition interventions may encounter challenges related to self-discipline, knowledge gaps, or the absence of personalized guidance. The lack of professional support could potentially lead to lower adherence rates, as individuals may find it more challenging to navigate the complexities of dietary changes on their own (487,496–498).

Connecting this perspective to the interventions examined in our thesis, policymakers might contemplate reimbursing the software designed for professionals, as tested in the trials conducted in Poland and the UK (see **Chapter 5** for details).

Exploring the idea of reimbursement for personalized nutrition interventions solely for individuals with obesity raises ethical concerns. This relates to the question about the fairness of providing reimbursement to this group to achieve weight loss when others can achieve it independently (499). It may look like healthy individuals bear the costs of obesity, which also resembles the principle of pooled health insurances, where high medical expenditures for one member are shared by all (257).

However, reimbursing interventions for individuals with obesity that enable them to adopt healthier activities may yield benefits not only for this subgroup but also for healthier individuals (within the health insurance pool) (499). This could manifest as lower health insurance premiums or reduced tax burdens due to an overall healthier pool. The social cost of subgroup reimbursement specifically to encourage healthier lifestyles may be offset by direct benefits to individuals and indirect advantages for the broader population. Note that this only applies if the savings in direct medical expenditures because of the interventions are higher than the increase in other (future) unrelated costs. Policymakers should consider these factors when devising reimbursement strategies.

Co-payment (partly reimbursed)

Policymakers could implement a price strategy based on the perception that people associate the cost of personalized nutrition services with their quality (487). This idea is elaborated

in the 'cost considerations' subsection. While individuals are willing to pay for personalized nutrition, it should however be reasonably priced. One solution is to partially subsidize the costs, creating incomplete health insurance coverage (i.e., co-payment) (500,501). However, introducing co-payments must be done with caution, as the potential limitations relate to decreased healthcare access for those in need (55).

In practical terms, part of the PREVENTOMICS interventions could be considered for reimbursement. For example, reimbursement could contain a general reimbursement amount (e.g., 20% of the total intervention costs or a fixed amount). Alternatively, reimbursement could target specific elements, such as dietitian sessions, the tests for personal information gathering (e.g., blood, urine, and saliva) or only the digital component (platform and app usage). Reimbursing digital interventions is something that was already introduced in Germany with the Digital Healthcare Act for reimbursing digital health technologies, like obesity apps as explained in **Chapter 8** (437). Policymakers should consider this when deciding how to apply co-payments.

Pricing strategies

In addition to reimbursement strategies, policymakers must also carefully consider pricing strategies (501,502). When developers adopt a cost-driven pricing approach, where the product's costs dictate the price, there is a tendency to overlook the product's inherent value (501,503). In this regard, alternative pricing strategies such as value-based pricing and performance-based pricing become important. These strategies have already been discussed in the literature in relation to another closely related research area: personalized medicine (34,501,503,504). These discussions in literature were further applied to personalized nutrition interventions in the text below.

In value-based pricing, the consumer's perception of the value of a product holds significant weight when determining its price (501,504). Applying this strategy to personalized nutrition interventions requires a thorough understanding of what 'value' signifies to consumers in this context. Beyond (cost)-effectiveness, a broader spectrum of 'value' should be examined, encompassing factors like unmet needs, societal advantages, and the burden of obesity as foundational elements for directing price negotiations (505). This thesis identified additional elements crucial to consumers, such as price of the intervention, user-friendliness, and data protection. Additionally (and not mentioned earlier in this thesis), the often-overlooked 'value of knowing' or 'personal utility' is paramount in personalized healthcare (501). In other words, personalized healthcare substantially reduces uncertainty regarding the likelihood of benefit. As interventions are tailored, individuals receiving them experience a psychological benefit – a heightened peace of mind, secure in the knowledge that they are highly likely to benefit (501).

Determining the most relevant factors for value-based pricing strategies in personalized nutrition remains an essential area for future research, in which we made first steps with this thesis. Subsequent steps in value-based pricing involve assigning measurable value to

identified benefits, using tools like questionnaires to measure quality of life (501). Following this, a price is established, grounded in the quantified value delivered, ensuring alignment with perceived benefits and resonance with the target audience. Flexibility is integral to this pricing strategy, acknowledging that the value may evolve over time and vary by jurisdiction.

In performance-based pricing, the cost of a product or service is linked to its actual performance and the outcomes it achieves (503,504). Essentially, this approach necessitates a clear definition of specific metrics or outcomes that will define the success of interventions. This involves dialogues between payers and developers in early stages to reach consensus about those health outcomes and the necessary data that should be collected for this (504). Such proactive discussions in early stages are essential to facilitating the practical application of performance-based agreements for personalized nutrition (504).

Translating this pricing strategy to personalized nutrition, payers could establish arrangements wherein developers offer rebates if the intervention falls short of achieving predetermined weight reduction targets over a specified period. This approach facilitates the creation of a pricing structure aligned with the attainment of specific milestones or outcomes. Regular assessments of the personalized nutrition's performance against these predefined metrics are important, and pricing should be based upon the actual outcomes achieved. By doing so, the financial burden of upfront payments can be mitigated, and the risk, both financial and uncertainty-related, can be shared collaboratively between payers and providers (504).

A crucial point to note about these pricing strategies is that they do not need to be employed exclusively; policymakers could also consider a hybrid approach combining both methods (503,506). For example, a foundational price can be established using value-based principles, complemented by the incorporation of performance-based incentives or discounts when specific health goals are successfully attained. This allows for a nuanced and flexible pricing structure that combines the strengths of both value-based and performance-based approaches.

Financial incentives

To increase uptake of personalized nutrition interventions, policymakers should carefully consider the implementation of financial incentives. Various incentive designs were mentioned in the discussion in **Chapter 7** of this thesis. For example, one approach could involve offering a cash reward to participants upon the successful completion of a personalized nutrition intervention. This incentive design was preferred in a study by Molema et al. (426). Another innovative method to boost uptake and sustain weight loss is through a 'commitment lottery,' wherein winners are selected from all participants but can claim their prize (e.g., 100 euros) only if they have achieved their specified goals (427). Given the proven effectiveness of such commitment lotteries in promoting physical activity for up to 52 weeks (427), applying this incentive design for personalized nutrition interventions could potentially elevate their uptake

and enhance their overall effectiveness. Future research should investigate the implications of these incentives on the cost-effectiveness of interventions, considering potential increases in costs by giving financial incentives balanced against the potential gains in effectiveness due to increased uptake.

However, a study presents a contrasting perspective, revealing that an escalating financial reward for individuals with type 2 diabetes was associated with a diminishing willingness to participate in lifestyle programs (425). The study offers potential reasons for this paradoxical finding, suggesting that incentives may deter participation due to a perceived sense of obligation. Additionally, the financial threshold needed to convince participation to participate might exceed the limits set in the study, and participants might feel explicitly controlled or monitored if financially rewarded, leading to negative reactions (425).

Another study with somewhat similar results argues that the notion that 'paying more will never hurt' does not universally hold true (507). The study revealed preference heterogeneity towards incentive attributes, highlighting the need for personalized incentives. This is crucial to maximize population reach of weight control programs (e.g., personalized nutrition) and to reduce health disparities. This nuanced approach to incentives aligns with the advanced nature of personalized nutrition interventions (no one-size-fits-all approach). Incentive designs may need to be tailored as well for different types of individuals (507).

Therefore, before integrating incentives into personalized nutrition interventions, comprehensive research is needed. This entails the investigation of specific applications, needs, and effects of incentives in the context of personalized nutrition interventions. This kind of research will ensure that financial incentives result in increased benefits (i.e., increased uptake), preventing additional costs without enhancing effectiveness.

In conclusion of this subsection, various pricing and reimbursement strategies are available for policymakers (together with potential payers and developers) to contemplate during the early stages of developing personalized nutrition interventions. It is crucial to emphasize that these pricing and reimbursement strategies should be exclusively applied to proven effective personalized nutrition interventions, and further evidence on effectiveness needs enhancement. Additionally, a key consideration is that pricing and reimbursement strategies differ across countries and health services (501). Policymakers must carefully weigh country-specific and health service-oriented strategies and recognize that these may evolve over time.

Consideration of a broader approach

As emphasized in the introduction, the significance of recognizing physical activity as an important lifestyle factor in preventing non-communicable diseases (NCDs) (2,3,325) has been addressed in the thesis structure, which aligns with Matveyev's model. However, focusing solely on physical activity by incorporating it in the structure is insufficient. Therefore, this

subsection pays again attention to physical activity for prevention purposes and for reducing the burden of diseases.

In 2019, on average only 40% of adults in OECD countries met the WHO recommendation of at least 150 minutes of moderate-to-vigorous intensity physical activity per week, heightening the risk of NCD development (12). Hence, it is advisable to prioritize the improvement of physical activity on the policy agenda. Literature suggests that a multifaceted strategy, incorporating both diet and physical activity, is more likely to enhance overall health outcomes compared to single-based strategies (3,325). This includes outcomes like mortality risk and body fat reduction (3,325). While a single-focus approach may be more effective at targeting specific behaviors (dietary or physical activity), multifaceted strategies have the potential for greater weight loss, thereby contributing to the reduction of obesity and associated diseases (508). Policymakers should therefore consider promoting innovations that address both dietary habits and physical activity.

Drawing on the practical example of the PREVENTOMICS interventions, policymakers should engage in collaborative efforts with developers to seamlessly integrate features addressing (personalized) lifestyle elements comprehensively, potentially leading to more impactful outcomes. Moreover, policymakers should consider tailoring interventions based on gender differences. Subgroup analyses from **Chapter 5** suggest that personalized nutrition interventions targeting males may yield greater benefits compared to females. Prior research supports this finding, demonstrating that males exhibit more positive responses to dietary interventions (357–359). Additionally, literature suggests that males with higher incomes show greater willingness to invest in personalized nutrition (178). Furthermore, in nearly all countries, a higher proportion of males reported meeting the recommended 150 minutes of physical activity per week compared to females (12). These findings underscore the significance of prioritizing efforts to enhance physical activity, alongside dietary improvements, especially for females. On the other hand, prioritizing efforts in dietary improvements, alongside physical activity improvements, should be the focus by males. This gender-specific approach could potentially lead to more substantial health improvements.

Furthermore, the potential impact of personalized nutrition interventions, such as the PREVENTOMICS ones, extends beyond preventive measures by including individuals already dealing with NCDs. One reason to consider extending this scope lies in the results of a study by Perez-Troncoso et al. (389), which suggest that individuals with a higher prevalence of NCDs exhibit a heightened interest and WTP for advanced personalized nutrition approaches (i.e., interventions that used information such as blood tests for personalizing recommendations). This might lead to greater engagement with personalized nutrition interventions, potentially improving their (cost-)effectiveness.

Additionally, expanding the focus of personalized nutrition to include both prevention and the treatment/management of NCDs can help align interventions with policymakers' needs

(509). While the statement "prevention is better than cure" underscores the imperative to fundamentally reform policies, obstacles hinder policymakers in executing such reforms. For example, the difficulties in measuring (and seeing) benefits of prevention, especially within the typical electoral term of four to five years, hinders policymakers from prioritizing prevention (509). Utilizing personalized nutrition for the treatment/management of NCDs (e.g., for symptom management) may yield visible benefits within the election period and thereby address policymaker needs (386,510,511).

Consideration of a holistic approach

Policymakers should adopt a holistic perspective that goes beyond a 'singular' focus on lifestyle-oriented interventions (encompassing both diet and physical activity). This comprehensive approach extends to factors influencing the uptake, acceptance, and behavioral change associated with these interventions. For example, SES-related factors, as highlighted in the subsection 'subgroup reimbursement,' play a significant role in uptake of personalized nutrition interventions, which might in turn lead to health inequalities. It is, however, crucial to recognize that these SES-related factors go beyond financial considerations. While the subsection emphasized the importance of financial aspects, policymakers must investigate a broader spectrum of SES-related and unrelated factors, acknowledging the multifaceted nature of behavioral change (34,328,495).

Chen et al. (495) proposed a framework of factors influencing individual food choices. Three main categories of this framework include food-related factors (internal and external), individual differences (personal-state and cognitive factors), and society-related factors (cultural, economic, and political elements) (495). While PREVENTOMICS interventions primarily focused on individual differences, policymakers aiming for successful behavioral change must consider all factors proposed in the framework.

In considering the impact of 'culture' on the uptake of personalized nutrition interventions, it is important to acknowledge that various cultural barriers influence uptake (372,512). Specifically, there are cultural barriers that hinder the sharing of essential medical information (372). Additionally, diverse preferences for body size, characterized by different cultural profiles, are crucial to consider (512). Caution is necessary when addressing cultural norms related to body weight, as poorly implemented policies may lead to unforeseen consequences or social backlash (512). Recognizing that obesity can stem from systemic factors, policymakers face a crucial decision about whether to prioritize individual-level interventions or tackle societal-level causes of obesity (512). Policymakers could probably best consider a combination of both individual-level and (carefully) implemented population-based strategies (e.g., to tackle societal-level causes) (37,278,372,513).

Users of personalized nutrition

The success of personalized nutrition interventions depends on collaborative efforts from all stakeholders, with active participation from the end-users playing a crucial role. Two key considerations related to the users of personalized nutrition warrant discussion.

Perceptions and skills of dietetics professionals

First, when evaluating a personalized nutrition intervention tailored for the professional market, such as the PREVENTOMICS initiative that focused on 'software for nutrition professionals,' various challenges arise concerning the users, specifically dietetics professionals. Abrahams et al. (514) investigated the barriers and facilitators influencing the adoption of personalized nutrition and associated technologies among dietetics professionals. Notably, practitioners who seamlessly integrated personalized nutrition technologies identified themselves as entrepreneurs, perceived lower risks associated with genetic testing and assigned higher importance to biotechnology, particularly omics technologies.

Furthermore, users of personalized nutrition technologies perceived professional skills as less important in dietetics practice, implying that they considered additional professional skills unnecessary (514,515). Instead, the importance of a career framework was emphasized to maximize and utilize existing skills and knowledge among dietitians (514,516), coupled with a supportive working environment (517). This aligns with the finding from **Chapter 8**, in which it was stated that minimal training is required for adopting personalized nutrition interventions.

However, the adoption of personalized nutrition interventions needs enhancement if effectiveness of those interventions is proved (514). Collective efforts from developers, policymakers, and management will be needed to enhance uptake. These efforts relate to raising awareness of emerging biotechnologies among dietetics practitioners who have not incorporated personalized nutrition into their practice. Strategies include case examples, sharing success stories from early adopters, promoting research initiatives, and addressing negative perceptions held by non-practicing dietitians (514).

Moreover, individuals with higher levels of self-efficacy are more likely to use personalized nutrition interventions (514). This connection is attributed to the association between self-efficacy and proactive personality traits. Specifically, these proactive personalities exhibit higher levels of risk-taking behavior, goal orientation, and a drive for achievement (514). Since self-efficacy is contingent on tasks and situations, and can be enhanced through learning and experience, future considerations may involve targeted training programs to elevate self-efficacy levels among students in the field of nutrition and dietetics (514).

Medicalization

Second, potential users of personalized nutrition interventions encounter challenges associated with 'medicalization,' which therefore requires thoughtful consideration. Medicalization is defined by Sadler (518) as 'a process by which human problems become

defined and treated as medical problems'. Obesity, classified as a disease within the medical field (513), undergoes the process of medicalization, which presents both advantages and disadvantages (519). On the positive side, it brings attention to factors beyond individual control, potentially reducing social discrimination faced by those with obesity, as discussed in **Chapter 8** (519). Furthermore, it may foster the development of more effective weight management strategies through drug development (520). However, it also runs the risk of labeling individuals as 'sick' who may not perceive themselves as such or have no desire to lose weight (519). Additionally, concerns arise about the broader reach of drugs, contributing to rising healthcare costs and potential adverse effects (519,520).

Within this context, a critical examination of the definition of obesity becomes crucial, emphasizing the dysregulation of dietary intake, metabolism, and adipose tissue over solely relying on elevated BMI (513). This approach ensures that not everyone with a non-"normal" BMI is automatically classified as having a disease and qualifying for medical treatment. Recognizing the multifaceted nature of obesity calls for a comprehensive approach, involving not only medical treatment for affected individuals but also population-wide risk reduction measures (520). The decision to use anti-obesity drugs, such as semaglutide should ideally be personalized, carefully weighing the benefits and risks of all treatment options (520). This aligns with the ongoing discussion on prevention versus medical treatment, advocating for a balanced, personalized approach (513,519,520). In this context, lifestyle interventions (e.g., personalized nutrition) should form the foundation of obesity treatment, with medical treatment seen as a complement to lifestyle changes (521).

While the responsibility to define obesity and determine the focus on prevention versus medical treatment lies with professionals (i.e., potential users of personalized nutrition interventions) and policymakers, individuals with obesity (also potential users of personalized nutrition) play a crucial role in finding this balance. An ongoing partnership between the patient and clinician is recommended (521), highlighting the importance of personalized strategies where individuals actively shape their health journey. This collaborative approach ensures that interventions align with individual needs and preferences, fostering a more effective and sustainable path toward health and well-being.

FUTURE RESEARCH

This section outlines areas for future research related to different challenges faced in the field of personalized nutrition. Several of these challenges and research areas align with the literature on personalized medicine, as previously discussed - a field closely linked to personalized nutrition (33). It is crucial to underscore that numerous future research ideas outlined below primarily concern HTA researchers. However, the involvement of policymakers and developers is equally vital. Securing funding for research is an important aspect, requiring collaborative efforts from various stakeholders, emphasizing the interdependence of research initiatives, policymaking, and financial support.

Research areas related to economic evaluations

It is essential to note that adhering to a common HTA framework, such as employing a standard perspective for economic evaluations, is recommended for both personalized and non-personalized interventions (522). This ensures comparability in economic evaluations and fosters consistency in decision-making (522). However, beyond these foundational considerations, HTA of personalized interventions may encounter additional hurdles that warrant exploration and unfolds areas for future research. Below, we will discuss these hurdles and future research areas related to economic evaluations, covering aspects such as the choice of comparator, outcome and value elements, evidence generation, discount rates, and patient-level modeling.

Choice of comparator

An important area for future research involves carefully selecting the most appropriate comparator. Figure 9.1, introduced earlier in this discussion, illustrates variations in cost-effectiveness outcomes based on different comparators. The figure compares the personalized nutrition interventions (with or without a behavioral change program) from the PREVENTOMICS project with a 'no intervention' scenario. Notably, the 'no intervention' data was not derived from a randomized controlled trial (RCT). Instead, we assumed no measured effect, emphasizing a comparison to people's current eating habits. These comparisons revealed differences in cost-effectiveness outcomes. Incremental effectiveness and costs were higher when interventions were compared to 'no intervention' rather than a control. This highlights the impact of the chosen comparator on cost-effectiveness results and emphasizes the need for careful consideration in future research.

In the context of the PREVENTOMICS project's objective to assess the added value of a 'personalized' component, we believe that our cost-effectiveness analyses used the appropriate comparator. However, future research may explore alternative comparators, contingent upon the specific assessment question (e.g., prevention versus treatment purposes?) (523,524). While interventions are commonly compared against usual care, the variability of usual care across conditions, patient-practitioner dynamics, clinical sites, countries, and over time necessitates careful consideration (525). Therefore, it is imperative for future research to carefully select the most fitting comparator (or analyze interventions versus multiple comparators), acknowledging that there may be multiple suitable options. Potential alternatives include individuals' current eating patterns (as illustrated in Figure 9.1 with 'no intervention'), non-digital interventions as discussed in **Chapter 6**, or drug comparators like semaglutide. The choice of different comparators has the potential to impact cost-effectiveness outcomes positively or negatively.

In an ideal scenario, evidence supporting a selected comparator would be derived from an RCT (523). However, due to constraints in time and resources, achieving this ideal may not always be feasible, making indirect comparisons necessary. Techniques such as network meta-analyses can offer valuable insights in such situations. However, caution is warranted

because of excessive heterogeneity between literature studies (526,527). For example, in the integration of data from diverse literature studies on personalized nutrition, heterogeneity may manifest as variations in interventions, objectives (e.g., prevention versus treatment), target populations, and country-differences.

Choice of outcome and value elements

Clinical outcome measures

To comprehensively evaluate the cost-effectiveness of personalized nutrition interventions, the choice of outcome measures, particularly focused on 'weight loss,' is crucial. In our modeling studies (**Chapters 4-6**), BMI acted as a proxy for 'weight loss' due to its use in a validated economic model (see **Chapter 3**), offering flexibility in simulating personalized nutrition's impact. However, future research should explore how other outcomes relate to the cost-effectiveness of personalized nutrition, considering alternatives like body fat (194,325). Exploring additional outcomes associated with carbohydrate and lipid metabolism, influencing diseases like diabetes and atherosclerosis, could provide valuable insights into the comprehensive benefits of dietary management beyond changes in body weight (361). For interventions targeting health improvement in the general population (e.g., discussed in **Chapter 6**), alternative outcomes such as fruit and vegetable intake or scores like the Mediterranean Diet Adherence Score (MEDAS) (381) could be considered as well. The lack of supporting data in literature emphasizes the need for future research to investigate how diverse outcomes correlate with lifetime cost-effectiveness, possibly examining links to all-cause mortality and diet-related diseases.

Quality of life data

Beyond clinical health outcomes, quality of life data, crucial for cost-effectiveness modeling, was measured using the EQ-5D-5L over the trial period, as well as by including EQ-5D data (i.e., general population sex- and age-specific utilities and utility decrements) from literature. While recommended in most HTA guidelines (294), the question arises whether this questionnaire captures all relevant aspects. The Obesity and Weight Loss Quality of Life instrument (OWLQOL) (results provided in **Chapter 8)** could complement quality of life measurement in economic evaluations (454). This instrument offers valuable insights into the quality of life domains that are relevant to people with overweight and obesity (454).

Additionally, it is important to provide better (more detailed) insights into mental health since it is a crucial aspect for people with obesity (528) and something that is influenced by nutrition (529,530). Commonly used instruments like the EQ-5D only partially assess mental health, suggesting that they may not fully capture its impact on quality of life (531). To address this, sensitive instruments are necessary to measure the impact of mental health improvement on quality of life, which improvement could potentially be achieved with personalized nutrition interventions. Future research should therefore consider extending quality of life measurements with more specific mental health-related questionnaires, such as the Mental

Health Quality of Life questionnaire (MHQoL) (531). Including these measures would provide a more nuanced understanding of the holistic impact of personalized nutrition interventions.

Additional value elements

Moreover, as observed in the HTA Core model assessment of personalized nutrition interventions in **Chapter 8**, comprehensive healthcare decision-making involves more than just costs and effectiveness in terms of clinical parameters and quality of life. In this context, it was suggested to expand the HTA by means of multiple criteria decision analysis (MCDA) to systematically evaluate and rank ideas based on weighted criteria (i.e., value elements) (465). An MCDA allows to assess the relative value of interventions and support decision-making during product development (54). Future research conducted by HTA researchers could explore the incorporation of all relevant criteria in an MCDA, such as the inclusion of the budget impact of personalized nutrition interventions (532).

Another way of taking care of these additional value elements is to integrate them in economic evaluations (522). This allows explicitly to trade-off length of life (and quality of life) versus additional value elements. Quantifying extra value elements, along with estimating the change in the cost-effectiveness threshold with their inclusion, would offer insights into these trade-offs. These elements might include compliance, considering variations across societal groups, as well as 'personal utility,' reflecting the value of knowledge or hope associated with personalized interventions (522). This 'personal utility' element was also discussed in the subsection 'pricing strategies'. Additional research is needed to identify and clearly define all relevant value elements, along with determining appropriate methodologies how to measure these elements (522).

One additional factor to consider in economic evaluations is environmental spillovers, encompassing elements like pollution, climate change, and extreme events. These elements could influence costs and outcomes beyond those targeted by the interventions (533). The spillovers contribute to poorer health, emphasizing that the effectiveness of an intervention should extend beyond direct health-related quality of life gains to encompass environmental impacts (533). The environmental footprint of personalized nutrition interventions may be potentially lower than that of drugs (534,535), impacting cost-effectiveness when drugs are used as comparators. The integration of environmental spillovers into economic evaluations requires further methodological development.

In conclusion, selecting appropriate outcome measures and determining which value elements to include in economic evaluations for personalized nutrition interventions poses a challenge for future research. With this, HTA researchers must carefully consider the distinction between value to individuals and society, ensuring that healthcare decisions align with societal needs. It is recommended to align personalized nutrition interventions with standard outcomes advised by HTA guidelines to facilitate comparability (522,536). Scenario analyses could

explore additional outcome measures and value elements, providing a more comprehensive understanding of the broader impact of personalized nutrition interventions.

Evidence generation

The rapid discovery of biomarkers and the complex nature of treatment strategies in personalized nutrition present challenges (as well as opportunities) for future research in evidence generation (54). An early HTA in the initial phases of biomarker research can prevent further development of biomarkers that are unlikely to offer significant added value to society and facilitate the translation of promising biomarkers into practical applications (537). Future studies in personalized nutrition interventions should prioritize the role of early HTA for better healthcare outcomes at less cost. A close collaboration between clinical researchers and HTA researchers is needed in this early stage.

Additionally, the proper estimation of testing costs, such as costs for genetic testing, is a critical aspect in evidence generation. It is crucial to verify the accuracy of initially assumed testing costs in the relevant setting and to account for potential variations in costs across different laboratories (522). These considerations deserve due attention in future research. Furthermore, as already done in **Chapters 4-6**, uncertainty analyses are important to conduct when evidence is generated by expert judgment (522). Future research could thus see these chapters as a valuable guide, ensuring a thorough and nuanced understanding of evidence generation based on expert judgement in the context of personalized nutrition.

Discount rates

In contrast with literature on HTA in personalized medicine, which recommends using the discount rates recommended in national guidelines (522), there are discussions about an appropriate discount rate for personalized nutrition interventions. This discrepancy especially arises if personalized nutrition aims to prevent diet-related diseases instead of using those interventions for treatment purposes (34). As detailed in **Chapter 6**, health benefits of personalized nutrition (i.e., prevention) often appear in the distant future, which makes it an interesting area for HTA researchers to explore the adjustment of discount rates for prevention (384).

Patient-level modeling

In our cost-effectiveness studies (**Chapters 4-6**), we applied cohort modeling to estimate the lifetime cost-effectiveness of personalized nutrition interventions. However, the suitability of patient-level modeling, as discussed in the context of personalized medicine (54,522,538), should be considered in future research. Patient-level modeling allows for the exploration of diverse clinical pathways and seamless integration of patient history into analyses. This could potentially offer a valuable approach in this context. While it is crucial to address parameter and structural uncertainty, as emphasized in standard HTA guidance, special attention must be given to factors like patient heterogeneity and stochastic uncertainty when utilizing this modeling technique (522).

The decision to use patient-level modeling techniques depends on the specific decision context (522). In the early HTA of personalized nutrition interventions, the appropriateness of patient-level modeling is a key question. This is influenced by data requirements, computational demands, and available time and resources, which may be limited in the initial stages of intervention development (538,539). Moreover, the complexity of these models poses challenges in transparency, particularly in effectively communicating the structure, assumptions, and outcomes (538). The central question is whether this complexity, with its resulting detailed information, is needed in early HTA. Particularly, when the primary goal is not immediate decision-making but rather a strategic evaluation of possibilities. Future research, both for the early HTA of personalized nutrition interventions and HTA in later stages, should carefully weigh the trade-offs between model complexity and the level of detailed information necessary to effectively inform healthcare decision-making.

(Incomplete) HTA framework

The EUnetHTA HTA core model framework, originally designed for assessing pharmaceuticals, medical and surgical interventions, diagnostic technologies, and screening (78), requires expansion for emerging interventions such as personalized nutrition and related areas (i.e., digital and nutrition interventions). Given the increasing promotion of these topics to enhance health outcomes (540), it becomes imperative to adapt frameworks such as the HTA Core model to effectively address these areas. **Chapter 8** of this thesis highlighted various essential adjustments needed for this purpose.

Despite the conclusion of the EUnetHTA initiative, responsible for developing the HTA Core model, in September 2023, collaborative efforts across countries on HTA will continue (78,541). This continued collaboration is expected to thrive under the influence of the new HTA regulation. This regulation places a primary focus on fostering cooperation between medicine regulators and HTA bodies, specifically in the context of clinical assessments, joint scientific consultations, and the identification of emerging health technologies (541).

Given the fast evolving landscape of personalized nutrition and the imperative to tailor or establish HTA frameworks for areas related to it, there arises another recommendation for future research. This suggestion involves a continued commitment to collaboration for the evolution and enhancement of the HTA Core model framework.

Study populations

The last area for future research to be mentioned in this discussion relates to the scope of personalized nutrition interventions to encompass additional or refined study populations. As discussed previously in the subsection ‘Consideration of a broader approach’, one additional identified target population for personalized nutrition interventions involves individuals with NCDs. Another, not earlier mentioned, target population for personalized nutrition interventions could be ‘athletes’ (487). Future research concerning this additional population relates to evaluating whether personalized nutrition could be (cost)-effective in enhancing

the fitness and competitive performance of dedicated athletes, such as runners or cyclists (487). Adjustments in the personalized nutrition interventions studied in the PREVENTOMICS project may be necessary, and potential new trials should be undertaken to provide evidence for (cost)-effectiveness.

Moreover, harnessing the existing data from the PREVENTOMICS project enables a targeted focus on refining study populations with a specific emphasis on cost-effectiveness. For example, future research could concentrate on analyzing the cost-effectiveness of personalized nutrition interventions in individuals with a particular metabolic cluster or those demonstrating the highest acceptance rates. Expanding on this approach, latent class modeling, utilizing data obtained from DCEs as presented in **Chapter 7**, provides a method to explore the heterogeneity within preferences for personalized nutrition interventions. Future research employing latent class modeling could identify groups most willing to pay for and utilize personalized nutrition interventions (402,419). Subsequently, cost-effectiveness studies could be customized for these specific study populations. This would offer a nuanced understanding of the impact and viability of personalized nutrition interventions within diverse and refined populations.

Sample size and trial follow-up

Sample size and the duration of trial follow-up emerge as notable limitations in this thesis. The economic evaluations were conducted based on trials with limited sample sizes and brief follow-up periods (10 weeks to 4 months), creating challenges for drawing robust conclusions and necessitating cautious interpretation. While this is not a significant issue at this developmental stage, given the ‘early’ HTA nature of this thesis, it is imperative to recognize the need for subsequent research. This research should feature larger and longer trials, inclusive of intervention enhancements, before implementation decisions can be confidently reached. The importance of this lies in the fact that even slight variations in trial results could yield different conclusions regarding cost-effectiveness, as highlighted by the uncertainty analysis in **Chapters 4-6**. This situation becomes particularly relevant when dealing with minimal observed incremental QALYs, as illustrated by the personalized nutrition interventions discussed in **Chapters 4-6**. In simpler terms, slight changes in trial results may yield marginal differences in absolute terms for small observed incremental QALYs, but they can induce substantial changes in ICURs (542).

Literature also underscores that the most significant improvements through nutrition interventions often appear after the first six months (329). Moreover, changing habits related to eating, drinking, or activity behavior requires an average of 66 days, varying from 18 to 254 days to reach the limit of automaticity (543). This emphasizes the need for longer trials to capture the full effect of behavioral change. Besides, with more robust data resulting from longer and larger trials, additional subgroup analyses could be done, such as the exploration of cost-effectiveness within different metabolic clusters. This could further enhance the understanding of the (cost-)effectiveness of personalized nutrition interventions. Future

research should therefore prioritize large-scale trials with extended follow-ups for more developed personalized nutrition interventions. However, it is crucial to balance the desire for extended trial durations with the rapidly evolving landscape of personalized nutrition. Trials should not be excessively prolonged, considering that significant advancements in intervention approaches may emerge while the trial is running.

In the context of future research, conducting value of information (VOI) analyses becomes crucial given the financial investment involved with more research and the potential for limited useful findings. VOI analyses assess whether investing more resources, such as enlarging and extending trials, would reduce decision uncertainty (544). This is particularly important in this early stage of product development, allowing for an early determination of whether additional research or development is necessary (52,537,545,546). While VOI analyses are not yet commonly employed in the HTA literature of medical devices—an area closely related to personalized nutrition—they offer valuable insights into the value of further research and optimal study design (547). As a result, it is recommended for future research to conduct these VOI analyses.

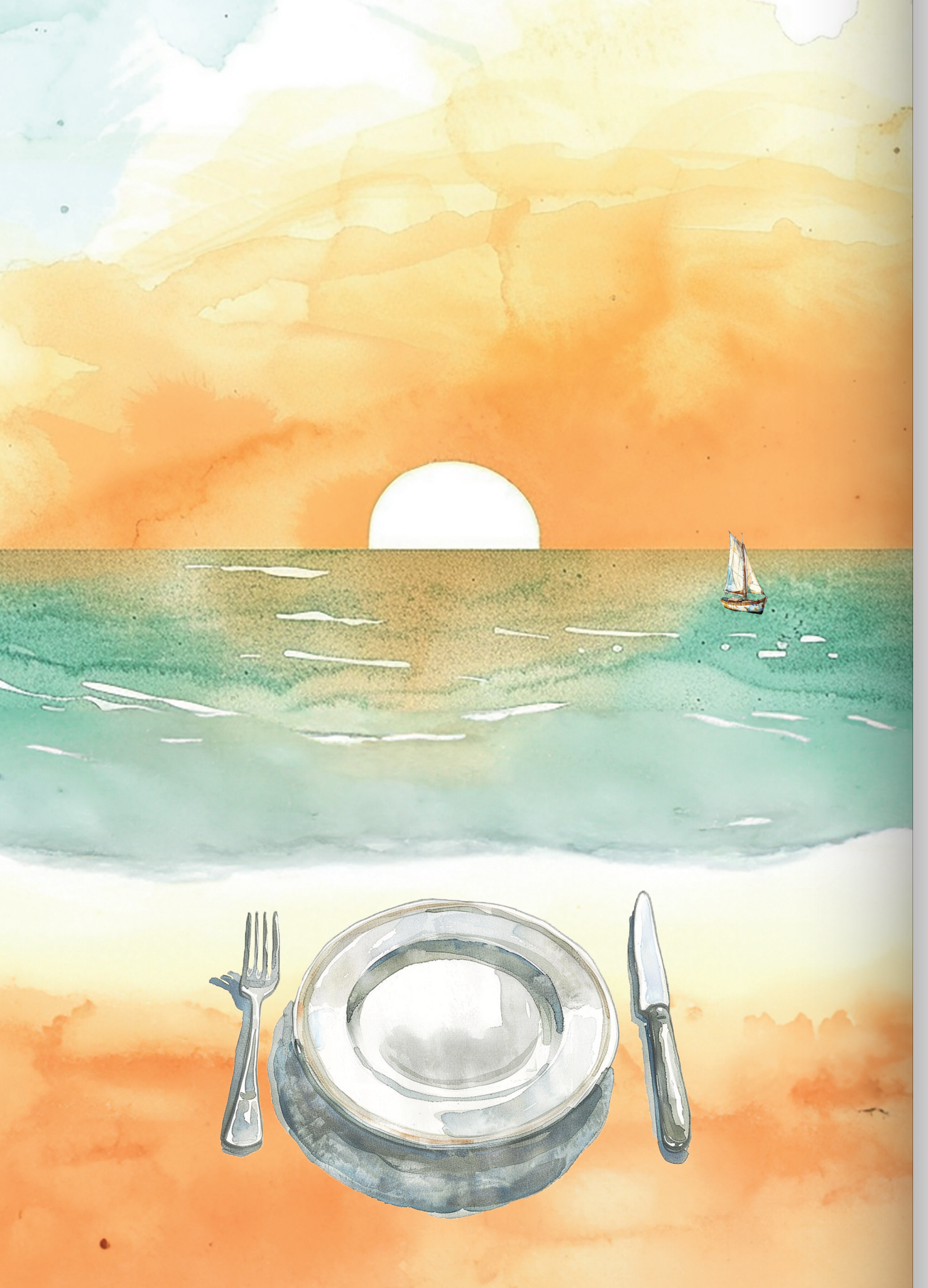
FINAL REMARKS

In summary, this thesis firmly establishes personalized nutrition as more than hype—it is a genuine hope with demonstrated potential. However, it is imperative to acknowledge that substantial groundwork is still needed before it can attain widespread market integration. The PREVENTOMICS interventions serve as an initial practical implementation of personalized nutrition, yet further research, development efforts, and policy initiatives are essential to foster increased uptake of these interventions and enhance overall impact.

This thesis represents a significant step in establishing the foundation for economic evaluations of personalized nutrition interventions in the preparation phase (Part I). Besides, (early) cost-effectiveness analyses were conducted in the competition phase (Part II). Moreover, this thesis extended the perspective on personalized nutrition interventions during the transition phase (Part III). This final phase included a comprehensive evaluation of the interventions, providing implications and recommendations for diverse stakeholders. The insights gained from this evaluation make a valuable contribution to the next cycle (i.e., preparation-competitions-transition) of development, implementation, and research concerning personalized nutrition interventions.

From this evaluation, it is essential to recognize that the complexity of assessing and implementing personalized nutrition goes beyond mere cost-effectiveness. It demands careful consideration of different aspects. Therefore, healthcare decisions regarding personalized nutrition should be tailored to the specific intervention, situation, and aligned with healthcare goals, acknowledging country differences, including cultural and health system variations. Besides, the multifaceted nature of personalized nutrition should not be underestimated. In

essence, while there are challenges ahead, personalized nutrition stands as a beacon of hope in shaping the future of healthcare.



Other

SUMMARY

English summary

Diseases such as ischemic heart disease (IHD), stroke, and diabetes, which are related to our diets, significantly contribute to global deaths. Consuming unhealthy foods and having overweight are major factors causing these diseases, resulting in substantial health and economic burdens. This underscores the urgent need for dietary improvements. Recognizing the diverse individual responses to nutrition calls for a shift from population-based dietary interventions to a more individualized one: 'personalized nutrition'.

The overarching aim of this thesis was to investigate the potential of personalized nutrition interventions through an early Health Technology Assessment (HTA). The initial step, outlined in Part I (preparation), involved conducting a systematic review of cost-effectiveness studies of interventions with a personalized nutrition component in adults (**Chapter 2**). Additionally, the potential impact of prevention, focusing on obesity, is assessed in **Chapter 3** and a newly developed Markov cost-effectiveness model is introduced.

Interventions developed through the PREVENTOMICS project served as examples of personalized nutrition interventions to be assessed in our early HTA. This project explored personalized nutrition interventions utilizing advanced technologies such as omics sciences. An ad-hoc developed platform was integrated into three different use cases: 1) a catering company, 2) a software for nutrition professionals, and 3) an e-commerce portal. These use cases underwent evaluation in trials conducted in Denmark, Spain, Poland, and the United Kingdom (UK). In Part II (competitions), economic evaluations compare these PREVENTOMICS interventions with a control group in terms of costs and effects (see **Chapters 4-6**). The model described in **Chapter 3** and trial results were used to estimate the lifetime cost-effectiveness of these interventions.

Expanding beyond cost-effectiveness alone, Part III (transition) of this thesis takes a broader HTA perspective. **Chapter 7** discusses results of discrete choice experiments (DCEs) to understand preferences of the general population regarding personalized nutrition interventions, and **Chapter 8** describes other crucial aspects related to HTA. The general discussion (**Chapter 9**) addresses implications for various stakeholders, and the question of whether personalized nutrition is a 'hope' or a 'hype.'

Part I – Preparation: establishing a foundation for cost-effectiveness analyses

In this first part, we found significant methodological variations among the 49 cost-effectiveness studies of personalized nutrition interventions identified in the systematic literature review (**Chapter 2**). The majority (91%) concentrated on psychological aspects of personalized nutrition, such as behavior and preferences. Quality-adjusted life year (QALY)

was the primary outcome measure in 32 studies. Variations in time horizons, comparators, and modeling assumptions played a significant role in the observed variations in costs and QALYs. Notably, 47% of the studies concluded that the intervention was cost-effective, and 75% of incremental cost-utility ratios (ICURs) fell below a willingness to pay (WTP) threshold of $50,000 per QALY. The majority of interventions were thus considered cost-effective.

Besides, most studies in the review (**Chapter 2**) predominantly centered on obesity, diabetes, or impaired glucose tolerance (IGT) (28 studies), potentially due to the substantial influence of these conditions on diet-related diseases. While it is recognized that diet-related diseases are not confined solely to individuals with these conditions, the importance of these health issues cannot be overstated. Hence, **Chapter 3** undertakes an in-depth examination of the lifelong health and economic consequences of obesity in five European countries. These analyses utilized a newly developed health economic model. Moreover, the potential impact of prevention is assessed in this chapter. This health economic model, which was a Markov model with different health states (diabetes, IHD, stroke and death), used body mass index (BMI) as a continuous parameter to give the model flexibility in simulating different impacts. Results indicated that, for the base-case scenario (i.e., healthy obese cohort, age 40 years, BMI 35 kg/m^2), total lifetime healthcare costs ranged from €75,376 in Greece to €343,354 in the Netherlands. Life expectancies varied from 37.9 years in Germany to 39.7 years in Spain. A one-unit decrease in BMI resulted in life expectancy gains (0.65 to 0.68 years) and changes in total healthcare costs ranging from -€1,563 to +€4,832. Conclusions underscored the substantial economic burden of obesity across the five countries. Decreasing BMI led to health benefits and lower obesity-related healthcare costs, but higher non-obesity-related healthcare costs. This emphasizes the importance of considering all costs in healthcare decision-making of preventive interventions.

Part II – Competitions: conducting cost-effectiveness analyses

Expanding upon the groundwork established in Part I, the focus now turns to the critical evaluation of the cost-effectiveness of PREVENTOMICS interventions. This assessment is crucial in response to the recommendation from **Chapter 2**, emphasizing the need to explore the cost-effectiveness of personalized nutrition interventions that integrate psychological and biological aspects of personalization, including the incorporation of omics sciences. This was an element overlooked in the previous studies, but which is inherently associated with higher costs.

The PREVENTOMICS interventions assessed in Part II are grounded in omics sciences. The assessment of cost-effectiveness utilized trial data to model the lifetime cost-effectiveness. The model outlined in **Chapter 3**, tailored for each country to align with the data from the PREVENTOMICS interventions, was used for this. In line with the recommendations from **Chapter 3**, all costs (considering a societal perspective) were included in the base-case

analyses, ensuring a comprehensive approach in the conducted cost-effectiveness analyses. Additionally, lifetime QALYs were employed as the measure of effectiveness.

The first PREVENTOMICS intervention, explored in **Chapter 4**, focused on how personalized nutrition interventions could be provided by a catering company. This involved a ten-week randomized controlled trial assessing the effectiveness of personalized home-delivered meals paired with a personalized behavioral change program (PP), compared to general home-delivered meals with a general behavioral change program (control) in Danish adults with overweight or obesity. At the end of the trial, no significant short-term effectiveness differences emerged between the PP and control groups, although wide confidence intervals were observed. Lifetime estimates indicated higher costs for the PP group compared to the control group (€1,736), along with a marginal gain in QALYs (0.011 QALYs). Consequently, a high ICUR of €158,798 per QALY gained was found, suggesting no cost-effectiveness. However, a 20% reduction in the intervention cost improved the potential for cost-effectiveness (ICUR €23,668 < WTP threshold €47,817). To enhance certainty regarding short-term effectiveness, it was recommended to conduct larger and/or longer trials.

The second PREVENTOMICS intervention, described in **Chapter 5**, focused on an intervention for nutrition professionals. In two four-month trials in Poland and the UK, personalized nutrition plans with (PP+B) or without (PP) a behavioral change program were compared with a control in adults with abdominal obesity and a BMI between 25 and 40 kg/m^2. While no significant differences in short-term effectiveness were observed in BMI and EQ-5D utilities, it is important to note that wide confidence intervals were once again observed. Lifetime analysis indicated potential cost-effectiveness in Poland (£20,404 per QALY for PP+B) and the UK (£13,006 for PP+B; £12,222 per QALY for PP). Base-case results of PP in Poland indicated that the intervention was not cost-effective (i.e., PP dominated by control), but sensitivity analyses suggested potential cost-effectiveness. A recurring recommendation was to reduce uncertainty regarding effectiveness results through the implementation of larger and/or longer trials.

The third PREVENTOMICS intervention, explored in **Chapter 6**, focused on an e-commerce portal. A four-month trial compared a personalized plan in which healthy individuals in Spain received a personalized categorized list of recommended food products (via the ALDI supermarket microsite), with (PP) or without (PN) a behavioral change program, with a control group. Both PP and PN showed slight differences in decreased BMI compared to the control over the trial period. However, lifetime cost-effectiveness analyses indicated no cost-effectiveness of PP and PN compared to control, with costs of €172,789 per QALY gained for PP and €50,108 per QALY gained for PN, compared to a €30,000 WTP threshold. Sensitivity analyses suggested potential cost-effectiveness if the interventions were given only to individuals with obesity. The interventions may offer a cost-effective approach for certain groups in Spain by reducing weight and lowering diet-related disease risks. However,

larger/longer trials are again recommended in this chapter for greater certainty regarding the effectiveness of the interventions.

Part III – Transition: to a broader health technology assessment perspective

This part uses a broader evaluation framework to evaluate personalized nutrition. It takes into account more than just cost-effectiveness as an important factor in healthcare decision-making. The transition is prompted by the execution of DCEs, detailed in **Chapter 7**. In this chapter, we investigated the factors influencing the uptake of personalized nutrition interventions and the WTP of the general population. Two DCEs, executed in four European countries and the United States, focused on personalized nutrition advice and personalized meals, involved over 500 respondents per country. The results underscore the important role of total nutrition expenditure in selecting personalized nutrition interventions. Participation rates were generally high (reaching up to 81% for 'personalized nutrition advice' and 87% for 'personalized meals' in Spain), with the highest WTP observed for six kilograms of weight loss. These findings indicate a willingness among individuals to invest in and engage with personalized nutrition interventions. However, the sensitivity to costs and the likelihood that the WTP of many respondents was lower than the actual intervention costs, suggest that policymakers should contemplate cost subsidies or financial incentives. Further research should explore the heterogeneity in preferences that was observed.

Chapter 8 shows that healthcare decision-making involves more than just cost-effectiveness and preferences. The HTA Core Model (EUnetHTA), which consists of a comprehensive methodological framework encompassing various domains for value assessment, was used to gather information and conduct an HTA. In addition to the previously mentioned (cost)-effectiveness and DCE results, the HTA revealed additional significant findings, particularly regarding minor safety concerns associated with personalized nutrition interventions. Moreover, ethical issues surrounding health inequality and the absence of specific legal regulations for personalized nutrition were identified. The chapter emphasizes the need for developers to explore (together with policymakers) financing options and to collaborate with policymakers to prevent exclusion of specific groups due to information shortages.

Beyond the specific recommendations derived from the HTA described in **Chapter 8**, overarching insights from various chapters in this thesis led to implications and recommendations for a diverse range of stakeholders. These are thoroughly discussed in the final chapter (**Chapter 9**: General discussion), which also includes recommendations for future research.

In summary, this thesis firmly establishes personalized nutrition as a genuine hope rather than a mere hype, demonstrating its potential. However, achieving widespread market integration necessitates substantial groundwork. While the PREVENTOMICS interventions represent an initial practical implementation, further research, development efforts, and policy initiatives are crucial for increased impact and uptake.

The general discussion provides valuable insights for the next cycle within Matveyev's model (i.e., preparation, competitions, and transition). In essence, implementing personalized nutrition requires the consideration of various aspects of specific interventions and situations, aligning with healthcare goals, and acknowledging country differences. Despite the challenges, personalized nutrition emerges as a beacon of hope in shaping the future of healthcare.

Nederlandse samenvatting

Ziekten gerelateerd aan onze voeding, zoals ischemische hartziekte, beroerte en diabetes, dragen aanzienlijk bij aan de sterfgevallen wereldwijd. Het consumeren van ongezonde voeding en het hebben van overgewicht zijn belangrijke factoren die deze ziekten veroorzaken. Dit resulteert in hoge gezondheids- en economische lasten en benadrukt de noodzaak voor verbeteringen in voeding. Het erkennen van de diverse individuele reacties op voeding, vraagt om een verschuiving van voedingsinterventies die zijn gebaseerd op de gehele bevolking naar een meer gepersonaliseerde aanpak: 'gepersonaliseerde voeding'.

Het overkoepelende doel van dit proefschrift was om de potentie van gepersonaliseerde voedingsinterventies te onderzoeken door middel van een vroege 'Health Technology Assessment' (HTA). De eerste stap, beschreven in Deel I (voorbereiding), bestond uit het uitvoeren van een systematische review van kosteneffectiviteitsstudies met betrekking tot interventies uitgevoerd bij volwassenen, die een component van gepersonaliseerde voeding bevatten (**Hoofdstuk 2**). Daarnaast wordt de potentiële impact van preventie gericht op obesitas geëvalueerd in **Hoofdstuk 3** en wordt een nieuw ontwikkeld Markov kosteneffectiviteitsmodel geïntroduceerd.

Interventies die zijn ontwikkeld door het PREVENTOMICS project dienden als voorbeelden van gepersonaliseerde voedingsinterventies die in onze vroege HTA werden beoordeeld. Dit project verkende gepersonaliseerde voedingsinterventies die gebruik maakten van geavanceerde technologieën zoals 'omics sciences'. Een ad-hoc ontwikkeld platform werd geïntegreerd in drie verschillende 'use cases': 1) een cateringbedrijf, 2) een software voor voedingsprofessionals, en 3) een e-commerce portaal. Deze 'use cases' werden geëvalueerd in trials uitgevoerd in Denemarken, Spanje, Polen en het Verenigd Koninkrijk (VK). In Deel II (competities) worden deze PREVENTOMICS interventies in economische evaluaties vergeleken met een controlegroep (zie **Hoofdstukken 4-6**). Deze vergelijking heeft betrekking op de kosten en effecten. Het model beschreven in **Hoofdstuk 3** en de resultaten van de trials werden gebruikt om de kosteneffectiviteit van deze interventies te schatten over de gehele levensduur.

In Deel III (transitie) van dit proefschrift wordt een breder HTA-perspectief aangenomen, waarbij verder wordt gekeken dan enkel kosteneffectiviteit. **Hoofdstuk 7** bespreekt de resultaten van discrete keuze-experimenten ('discrete choice experiments', DCEs) om de voorkeuren van de algemene bevolking met betrekking tot gepersonaliseerde voedingsinterventies te begrijpen en **Hoofdstuk 8** beschrijft andere cruciale aspecten gerelateerd aan HTA. De algemene discussie (**Hoofdstuk 9**) behandelt implicaties voor verschillende belanghebbenden en de vraag of gepersonaliseerde voeding een 'hoop' of een 'hype' is.

Deel I - Voorbereiding: het leggen van een basis voor kosteneffectiviteitsanalyses

In dit eerste deel hebben we bij een systematische review grote methodologische verschillen gevonden tussen de 49 geïncludeerde kosteneffectiviteitsstudies van gepersonaliseerde voedingsinterventies (**Hoofdstuk 2**). De meerderheid (91%) concentreerde zich op psychologische aspecten van gepersonaliseerde voeding, zoals gedrag en voorkeuren. In 32 studies was het voor kwaliteit gecorrigeerde levensjaar ('quality-adjusted life year', QALY) de primaire uitkomstmaat. Verschillen in tijdshorizon, 'comparators' en modelaannames speelden een belangrijke rol in de waargenomen variaties in kosten en QALYs. Opvallend is dat 47% van de studies concludeerde dat de interventie kosteneffectief was en dat 75% van de incrementele kostenutiliteitsratio's ('incremental cost-utility ratios', ICURs) onder de drempel van de (maximale) bereidheid om te betalen ('willingness to pay', WTP) van $50.000 per QALY viel. De meeste interventies werden dus als kosteneffectief beschouwd.

Daarnaast richtten de meeste studies uit de review (**Hoofdstuk 2**) zich voornamelijk op obesitas, diabetes of verminderde glucosetolerantie ('impaired glucose tolerance', IGT) (28 studies). Dit is waarschijnlijk vanwege de aanzienlijke invloed van deze aandoeningen op voedingsgerelateerde ziekten. Hoewel erkend wordt dat voedingsgerelateerde ziekten niet alleen beperkt zijn tot individuen met deze aandoeningen, kan het belang van deze gezondheidsproblemen niet genoeg benadrukt worden. Daarom wordt in **Hoofdstuk 3** een diepgaand onderzoek gedaan naar de gezondheids- en economische gevolgen van obesitas in vijf Europese landen over de gehele levensduur. Deze analyses maakten gebruik van een nieuw ontwikkeld gezondheidseconomisch model. Daarnaast wordt in dit hoofdstuk de potentiële impact van preventie beoordeeld. Dit gezondheidseconomische model was een Markov model met verschillende gezondheidstoestanden (diabetes, ischemische hartziekte, beroerte en overlijden). Het model gebruikte de 'body mass index' (BMI) als een continue parameter om flexibiliteit te creëren in het simuleren van de impact. De resultaten gaven aan dat in het 'base-case' scenario (d.w.z. een gezond cohort met obesitas, leeftijd 40 jaar, BMI 35 kg/m^2) de totale kosten voor de gezondheidszorg over de gehele levensduur varieerden van €75.376 in Griekenland tot €343.354 in Nederland. De levensverwachting varieerde van 37,9 jaar in Duitsland tot 39,7 jaar in Spanje. Een daling van de BMI met één eenheid resulteerde in een stijging van de levensverwachting (0,65 tot 0,68 jaar) en veranderingen in de totale kosten voor de gezondheidszorg die varieerde van -€1.563 tot +€4.832. De conclusies benadrukten de aanzienlijke economische last van obesitas in de vijf landen. Een dalende BMI leidde tot gezondheidsvoordelen en een verlaging van de aan obesitas gerelateerde zorgkosten. Echter leidde het ook tot een stijging van de niet-obesitas gerelateerde zorgkosten. Dit benadrukt het belang van het meenemen van alle kosten in de besluitvorming rondom preventieve interventies in de gezondheidszorg.

Deel II – Competities: het uitvoeren van kosteneffectiviteitsanalyses

Voortbouwend op de basis die in Deel I is gelegd, richt dit tweede deel zich op de kritische evaluatie van de kosteneffectiviteit van de PREVENTOMICS interventies. Deze evaluatie is cruciaal als reactie op de aanbeveling uit **Hoofdstuk 2**. Deze aanbeveling benadrukt de noodzaak om de kosteneffectiviteit van gepersonaliseerde voedingsinterventies die psychologische en biologische aspecten van personalisatie integreren, inclusief de integratie van 'omics sciences', te onderzoeken. Dit was een element dat in eerdere studies over het hoofd werd gezien, maar dat inherent gepaard gaat met hogere kosten.

De PREVENTOMICS interventies die in Deel II zijn geëvalueerd, zijn gebaseerd op 'omics sciences'. Bij de evaluatie van de kosteneffectiviteit werd gebruik gemaakt van trial data om de kosteneffectiviteit over de gehele levensduur te modelleren. Hiervoor werd gebruik gemaakt van het model dat in **Hoofdstuk 3** is beschreven. Dit model werd aangepast voor elk land om overeen te komen met de data van de PREVENTOMICS interventies. In lijn met de aanbevelingen uit **Hoofdstuk 3,** zijn alle kosten (vanuit een maatschappelijk perspectief) meegenomen in de 'base-case' analyses. Op deze manier werd ervoor gezorgd dat de kosteneffectiviteitsanalyses op een uitgebreide en grondige manier werden uitgevoerd. Daarnaast werden QALYs over de gehele levensduur gebruikt als maatstaf voor de effectiviteit.

De eerste PREVENTOMICS interventie, die in **Hoofdstuk 4** is onderzocht, richtte zich op hoe gepersonaliseerde voedingsinterventies konden worden aangeboden door een cateringbedrijf. In een 'randomized controlled' trial van tien weken werd de effectiviteit van gepersonaliseerde thuisbezorgde maaltijden samen met een gepersonaliseerd gedragsveranderingsprogramma ('personalized plan', PP) vergeleken met de effectiviteit van een controle interventie. Deze controle interventie bestond uit niet-gepersonaliseerde (d.w.z. algemene) thuisbezorgde maaltijden met een algemeen gedragsveranderingsprogramma. Dit onderzoek werd uitgevoerd bij Deense volwassenen met overgewicht of obesitas. Aan het einde van de trial periode werden geen significante verschillen in effecten tussen PP en de controlegroep gevonden. Echter werden er wel brede betrouwbaarheidsintervallen waargenomen. De schattingen die werden gedaan over de gehele levensduur toonden hogere kosten voor de PP groep in vergelijking met de controlegroep (€1.736), samen met marginaal positieve incrementele QALYs (0,011 QALYs). Hierdoor werd een hoge ICUR van €158.798 per QALY gevonden, wat suggereert dat PP niet kosteneffectief is. Een verlaging van de interventiekosten met 20% verbeterde echter wel de potentie voor kosteneffectiviteit (ICUR €23.668 < WTP-drempel €47.817). Om de zekerheid rondom de effectiviteit op de korte termijn te vergroten, werd aanbevolen om grotere en/of langere trials uit te voeren.

De tweede PREVENTOMICS interventie, beschreven in **Hoofdstuk 5**, richtte zich op een interventie voor voedingsprofessionals. In twee trials van vier-maanden in Polen en het VK

werden gepersonaliseerde voedingsplannen met ('personalized plan plus behavioral change', PP+B) of zonder ('personalized plan', PP) een gedragsveranderingsprogramma vergeleken met een controle interventie bij volwassenen met abdominale obesitas en een BMI tussen de 25 en 40 kg/m2. Hoewel er geen significante verschillen in effectiviteit op de korte termijn werden waargenomen in BMI en EQ-5D utiliteiten, is het belangrijk om te benoemen dat er opnieuw brede betrouwbaarheidsintervallen werden waargenomen. Analyses met een levenslange follow-up duidden op mogelijke kosteneffectiviteit in Polen (£20.404 per QALY voor PP+B) en het VK (£13.006 voor PP+B; £12.222 per QALY voor PP). 'Base-case' resultaten van PP in Polen werden als niet kosteneffectief beschouwd (d.w.z. PP werd gedomineerd door de controle arm), maar gevoeligheidsanalyses suggereerden potentiële kosteneffectiviteit. Een terugkerende aanbeveling was om onzekerheid met betrekking tot effectiviteit te verminderen door de implementatie van grotere en/of langere trials.

De derde PREVENTOMICS interventie, die in **Hoofdstuk 6** is onderzocht, richtte zich op een e-commerce portaal. In een vier-maanden durende trial werd een gepersonaliseerd plan waarbij gezonde individuen in Spanje een gepersonaliseerde gecategoriseerde lijst met aanbevolen voedingsproducten ontvingen (via de microsite van de ALDI-supermarkt), met ('personalized plan', PP) of zonder ('personalized nutrition', PN) een gedragsveranderingsprogramma, vergeleken met een controlegroep. Na de trial periode, toonden zowel PP als PN lichte verschillen in BMI-afname vergeleken met de controle interventie. Echter, kosteneffectiviteitsanalyses over de gehele levensduur gaven aan dat PP en PN niet kosteneffectief waren vergeleken met de controle interventie, met kosten van €172.789 per gewonnen QALY voor PP en €50.108 per gewonnen QALY voor PN (WTP-drempel €30.000). Gevoeligheidsanalyses suggereerden potentiële kosteneffectiviteit als interventies alleen zouden worden gegeven aan individuen met obesitas. De interventies kunnen een kosteneffectieve aanpak bieden voor bepaalde groepen in Spanje door gewicht te verminderen en de risico's op voedingsgerelateerde ziekten te verlagen. Echter, grotere/langere trials worden in dit hoofdstuk opnieuw aanbevolen voor grotere zekerheid ten aanzien van de effectiviteit van de interventies.

Deel III – Transitie: naar een breder 'health technology assessment' perspectief

In dit deel wordt een breder evaluatiekader gehanteerd om gepersonaliseerde voeding te evalueren. Hierbij wordt verder gekeken dan alleen kosteneffectiviteit als belangrijke factor bij de besluitvorming in de gezondheidszorg. Dit wordt ingeleid door de uitvoering van DCEs die zijn beschreven in **Hoofdstuk 7**. In dit hoofdstuk worden de factoren onderzocht die van invloed zijn op de acceptatie van gepersonaliseerde voedingsinterventies en de WTP van de algemene bevolking. In twee DCEs, uitgevoerd in vier Europese landen en de Verenigde Staten, gericht op gepersonaliseerd voedingsadvies en gepersonaliseerde maaltijden, waren ruim 500 respondenten per land betrokken. De resultaten benadrukken de belangrijke rol van de totale voedingsuitgaven bij het selecteren van gepersonaliseerde voedingsinterventies.

De deelnamepercentages waren over het algemeen hoog (tot 81% voor 'gepersonaliseerd voedingsadvies' en 87% voor 'gepersonaliseerde maaltijden' in Spanje) en de hoogste WTP werd waargenomen voor zes kilogram gewichtsverlies. Deze bevindingen duiden op de bereidheid van individuen om te investeren in en deel te nemen aan gepersonaliseerde voedingsinterventies. Echter, de gevoeligheid voor kosten en de waarschijnlijkheid dat de WTP van veel respondenten lager was dan de daadwerkelijke interventiekosten, suggereren dat beleidsmakers kostensubsidies of financiële prikkels zouden moeten overwegen. Verder onderzoek zou de waargenomen heterogeniteit in voorkeuren moeten analyseren.

Hoofdstuk 8 laat zien dat besluitvorming in de gezondheidszorg meer inhoudt dan alleen kosteneffectiviteit en voorkeuren. Het HTA Core Model (EUnetHTA), dat bestaat uit een alomvattend methodologisch raamwerk dat verschillende domeinen voor 'waarde beoordeling' bevat, werd gebruikt om informatie te verzamelen en een HTA uit te voeren. Naast de eerdergenoemde (kosten)effectiviteits- en DCE-resultaten, onthulde de HTA aanvullende belangrijke bevindingen, met name met betrekking tot kleine veiligheidsproblemen die verband houden met gepersonaliseerde voedingsinterventies. Daarnaast werden ethische kwesties rondom ongelijkheid op gezondheidsgebied en het ontbreken van specifieke wettelijke regelgeving voor gepersonaliseerde voeding geïdentificeerd. Het hoofdstuk benadrukt de noodzaak voor ontwikkelaars om (samen met beleidsmakers) financieringsopties te verkennen en samen te werken met beleidsmakers om uitsluiting van specifieke groepen als gevolg van informatietekorten te voorkomen.

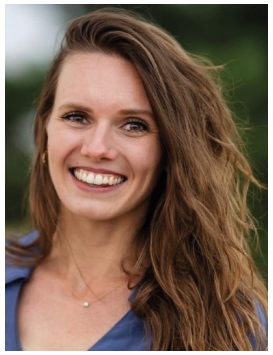
Naast de specifieke aanbevelingen die voortkwamen uit de HTA beschreven in **Hoofdstuk 8**, hebben overkoepelende inzichten uit verschillende hoofdstukken in dit proefschrift geleid tot implicaties en aanbevelingen voor een breed scala aan belanghebbenden. Deze worden uitvoerig besproken in het laatste hoofdstuk (**Hoofdstuk 9**: Algemene discussie), waarin ook aanbevelingen voor toekomstig onderzoek worden opgenomen.

Samenvattend, laat dit proefschrift met de potentie van gepersonaliseerde voeding zien dat dit niet enkel gezien kan worden als een 'hype', maar ook als een echte 'hoop'. Voor het verwezenlijken van een wijdverspreide integratie in de markt is echter aanzienlijk voorbereidend werk nodig. Hoewel de PREVENTOMICS interventies een eerste praktische implementatie vertegenwoordigen, zijn verder onderzoek, ontwikkelingsactiviteiten en beleidsinitiatieven cruciaal voor een grotere impact en toepassing.

De algemene discussie levert waardevolle inzichten op voor de volgende cyclus binnen het model van Matveyev (d.w.z. voorbereiding, competities en transitie). In wezen vereist het implementeren van gepersonaliseerde voeding de overweging van verschillende aspecten van specifieke interventies en situaties, in lijn met de gezondheidszorgdoelstellingen en met erkenning van de verschillen tussen landen. Ondanks de uitdagingen komt gepersonaliseerde voeding naar voren als een baken van hoop bij het vormgeven van de toekomst van de gezondheidszorg.

PORTFOLIO

About the author



Milanne Galekop was born in IJsselstein on August 27, 1995. She began her academic journey in 2013 by enrolling in the bachelor's program 'Beleid en Management Gezondheidszorg' at the Erasmus University in Rotterdam. After earning her Bachelor of Science degree in 2016, she pursued and obtained a Master of Science degree in Health Economics, Policy and Law (specialization: Health Economics) from the same university in 2018. During her studies, Milanne worked as a student assistant at the Erasmus School of Health Policy and Management (ESHPM). She worked on her first paper, which stemmed from her bachelor thesis, and completed an internship at Novartis Nederland. These experiences ignited her interest in working in academia and health technology assessment. In early 2019, Milanne started as a PhD candidate at ESHPM, under the supervision of Carin Uyl-de Groot and Ken Redekop. Her research focused on the early health technology assessment of personalized nutrition interventions as part of PREVENTOMICS, a European Horizon 2020 project. This topic perfectly combined her academic interests with her personal passion for nutrition and sports. Throughout her PhD, Milanne actively contributed to education, lecturing courses, coordinating the bachelor's thesis program, and guiding master's thesis students at ESHPM. Additionally, she served as a board member of the ISPOR student chapter at ESHPM. Milanne is dedicated to advancing the field of health technology assessment, with the goal of enhancing healthcare, including prevention, to improve patient health.

Publications

Included in this PhD thesis

A Systematic Review of Cost-Effectiveness Studies of Interventions with a Personalized Nutrition Component in Adults.
Milanne M.J. Galekop, Carin A. Uyl-de Groot, W. Ken Redekop, Value in Health. 2021; 24 (3): 325-335. doi.org/10.1016/j.jval.2020.12.006

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Courses

2019	Presentation design and skills
2019	Systematic literature retrieval: PubMed, Embase and other databases
2019	How to finish your PhD in time
2019	Professionalism and integrity in research
2019	LinkedIn workshop
2019	ISPOR poster workshop
2019	Statistical methods for health economics & outcomes research
2019	Cost-effectiveness analysis alongside clinical trials
2019	Choice modelling and stated choice survey design
2020	Coachvaardigheden
2020	English academic writing for PhD candidates
2021	Using R for decision modeling in health technology assessment
2021	Dilemma game
2021	Decision modeling for health economic evaluation (advanced)
2022	BKO deelcertificaat delivery
2022	Your next step

Conferences

2019	lolaHESG conference
2019	ISPOR annual European conference, poster presentation
2020	ISPOR annual European conference, poster presentation
2022	lolaHESG conference, paper discussion
2022	EUHEA PhD conference, paper discussion
2022	ESPEN conference, poster presentation
2022	ISPOR annual European conference, poster presentation
2023	lolaHESG conference, paper discussion

Teaching

2019	Statistiek A, pre-master
2020	Statistiek A, pre-master
2020	Honours program, bachelor
2020	Coach afstudeerproject, bachelor
2020	Coordination afstudeerproject, bachelor
2020	NIHES health economics summer course
2021	Honours program, bachelor
2021	Coach afstudeerproject, bachelor
2021	Blok 5 technologie en innovatie, bachelor
2021	Health technology assessment practical, master
2022	Honours program, bachelor
2022	Master thesis
2022	Coach afstudeerproject, bachelor
2022	Bachelor opendag
2022	Interprofessioneel onderwijs, bachelor EMC
2022	Blok 5 technologie en innovatie, bachelor
2022	Health technology assessment practical, master
2023	Honours program, bachelor
2023	Master thesis
2023	Coach afstudeerproject, bachelor

Other

2020-2022	President ISPOR student chapter Rotterdam
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