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ORIGINAL RESEARCH ARTICLE

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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Abstract

Background 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: €1736) 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).

Conclusion 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.

Trial Registration Number ClinicalTrials.gov registry (NCT04590989).

1 Introduction

Overweight [body mass index (BMI) ≥ 25 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) are growing public health problems [1]. Globally, the prevalence of obesity has nearly tripled between 1975 and 2016 [1]. 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 [2]. Additionally, in 34 out of 36 OECD member countries, more than half of the population is now overweight [2]. 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 [1]. These diseases and obesity itself will reduce the average life expectancy by 2.7 years across OECD countries over the period 2020–2050 [2]. 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) [3–5], people may be hampered in their capacity to perform their daily activities. Altogether, these negative physical and mental

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Key Points for Decision Makers

We found that the short-term effectiveness of a personalized nutrition plan compared with a non-personalized plan was limited. However, we saw that there was large uncertainty regarding effectiveness, which could be reduced by making trials longer or larger.

The combination of modest short-term effectiveness and the extra costs of personalization resulted in unfavorable cost-effectiveness estimates over a lifetime. Scaling up personalized nutrition interventions would reduce per-patient costs and thereby make them more cost-effective.

conditions reduce health-related quality of life (HRQoL) [6, 7]. Fortunately, studies have shown that weight loss is associated with improved HRQoL [7–9].

In addition to the huge global health problems caused by overweight and obesity, these conditions also pose a serious threat to the economy [2]. On average, 8.4% of the health budget of OECD countries is spent on treating the consequences of obesity [2, 10]. In the USA this number is even higher, at 14% of the health budget [2]. Besides healthcare costs, obesity has a rising impact on other social costs as well, such as patient and family costs and productivity losses [11, 12]. Lifetime productivity losses are almost twice as high in the obesity population compared with normal weight populations [11].

A well-balanced healthy diet is one of the key factors to prevent overweight, obesity, and related diseases [2]. Several studies showed relationships between dietary patterns and significant changes in BMI over time [13–15]. Countries have therefore implemented different policies to tackle overweight and obesity, including those targeting diets [2]. However, obesity is a complex multifactorial disorder, which makes its management a challenging task [16]. 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 [17–19]. Therefore, there is an increasing demand for studies investigating personalized nutrition approaches, rather than approaches on a population level [20]. Personalized nutrition could be defined as "an approach that uses information on individual characteristics to develop targeted nutritional advice, products or services" [20]. Several studies have already proven the effectiveness of personalized nutrition, but they have not yielded consistent findings [21, 22]. 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) [23]. 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 [25]. 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) [25, 26]. 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 [26]. Effectiveness results showed that the PP intervention did not significantly improve health measures beyond those produced by the control (non-personalized) intervention [27]. However, the wide confidence intervals (CIs) around the effectiveness estimates (e.g., effect in BMI of PP versus control: −0.07, CI 95% −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 [28]. This is, however, especially crucial to evaluate, given the potentially higher estimated costs of using omics technologies to personalize interventions [29]. 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.

2 Methodology

2.1 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 [30]. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was followed [31].

2.2 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) [26, 27].

2.3 Trial Description

The Danish trial was a 10-week randomized, single-center, parallel-group, double-blinded intervention study [26, 27]. 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 [25]. 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 [26, 27]. 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 [26, 27]. Both groups received meals that were isocaloric and complied with the national dietary guidelines on macronutrient distribution [32]. 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 [33]. 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' [26]. 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) [26]. See Supplement 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 [26].

2.4 Short-Term Costs and Effects

2.4.1 Effects

Different health outcomes were derived from measurements at baseline and follow-up, of which BMI was one [27]. Information about quality of life was also measured by the EuroQol five-dimension questionnaire with five levels (EQ-5D-5L) [34]. 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 [35, 36]. The EQ-5D-5L also includes a Visual Analogue Scale (EQ VAS), by which respondents report their perceived health status [35].

Statistical analyses were performed using STATA 17 software [37]. 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) [38]. 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 $\alpha = 0.05$. Restricted maximum likelihood (REML) was used to fit LMMS to accommodate missing values at random within a single response variable among the participants' data [39]. 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 [40–42]. 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.

2.4.2 Costs

Costs were considered from a societal perspective, as proposed in the Danish standards for economic evaluations [43, 44], but only intervention costs were assumed relevant societal costs over the trial period [45]. 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 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.[27], and the prices per kilogram were 3.84€, 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 [25]), 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).

2.5 Long-Term Cost-Effectiveness

2.5.1 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 [30]. The model was developed as part of a European Union (EU)-funded project (COMPAR-EU) [46]. Figure 1 provides an overview of the model's structure [30]. Each rectangle shows a different health state. The model starts with a cohort of people with overweight or obesity and a certain distribution in men/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 [47, 48]. 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,

Table 1 Average intervention costs per participant (2020 €; 2020 DKK in brackets)

Components	PP	Control	Difference
(1) Meals (breakfast and dinner, eaten 6 days per week)			
Direct costs			
Food costs	2746 (20,507)	2746 (20,507)	0
Packaging costs	1239 (9253)	1239 (9253)	0
Production costs	1273 (9507)	318 (2375)	955 (7132)
Delivery costs	189 (1411)	189 (1411)	0
Indirect costs (25% of direct costs)[a]	1362 (10,171)	1123 (8,387)	239 (1784)
Functional ingredients	5.00 (37.39)	0	5.00 (37.39)
Total meal costs	*6814 (50,887)*	*5616 (41,940)*	*1198 (8947)*
(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 + questionnaire maintenance)[b]	0.81 (6.02)	0.81 (6.02)	0
(5) Tests (blood, urine, saliva)			
Omics	383 (2857)	0	383 (2857)
Genetics	54 (403)	0	54 (403)
Other (e.g., overhead)	115 (857)	0	115 (857)
Total tests costs	*551 (4117)*	*0*	*551 (4117)*
TOTAL COSTS	**7402 (55,277)**	**5653 (42,215)**	**1749 (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 ($N = 400$)

higher for patients in the diabetes state than patients in the 'no diabetes/no IHD/no stroke' state [30]. 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 [30].

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 [30].

2.5.2 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 2; details are described elsewhere [30].

2.5.2.1 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 [49]. The sex-specific relative risks for the association between BMI and all-cause mortality were obtained from a meta-analysis of 230 cohort studies [50]. The Global Burden of Disease study was used for the relative risks by age for the association between BMI and diabetes, IHD, and stroke [49]. 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 [51–53]. 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 [51, 52]. Moreover, three additional studies [54–56] and OECD data were used to calculate mortality [57, 58]. No fixed transition probabilities are given in Table 2 since they varied according to age, sex, and BMI [30].

2.5.2.2 Effectiveness The mean change in BMI was used as one of the intervention effects and was obtained from the Danish trial [27]. Since this change was observed over the

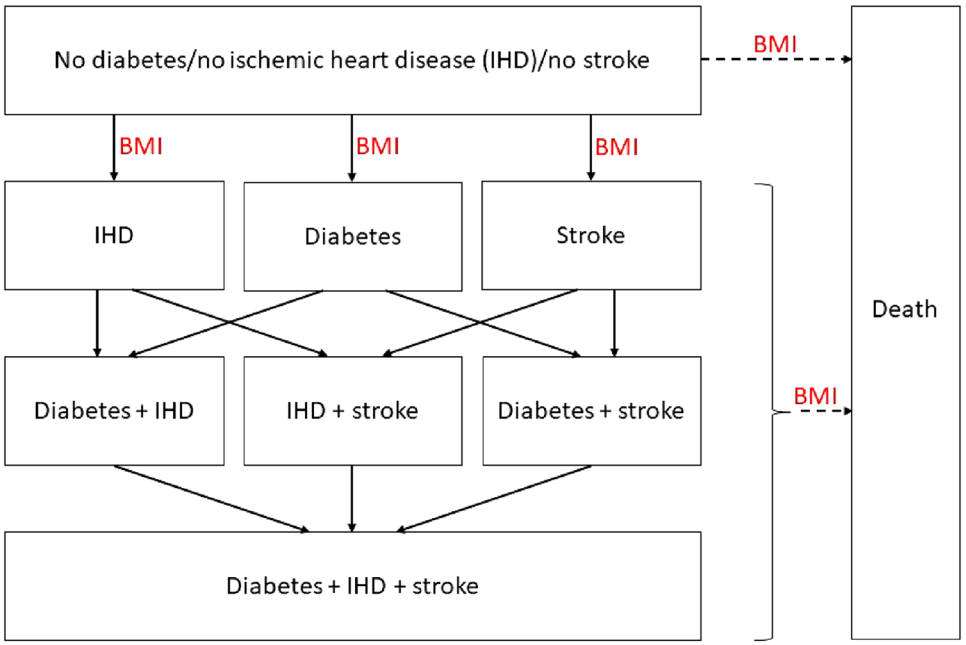


Fig 1 Structure of the Markov model for obesity as described by Hoogendoorn et al.[30]. *BMI* body mass index, *IHD* Ischemic heart disease

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.[59], 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 2) [59]. 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 [60, 61]. 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 Sect. 2.4.1). The long-term health outcomes, as recommended in the guideline [43, 44], were expressed in life expectancy and quality-adjusted life years (QALYs), which were estimated using the model [30]. HRQoL in the model was based on general population sex- and age-specific utilities, based on EQ-5D values in Denmark [62]. These utilities were adjusted for the occurrence of diabetes, IHD, and stroke using prevalence data and previously published utility decrements for the different diseases [63]. All utilities were discounted at 4% per year [43, 44, 64].

2.5.2.3 Costs Total costs of the intervention (see section 2.4.2) 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 [64–67].

Costs of productivity loss were estimated using SHARE data [68] on the basis of values for central European countries since the employment status in Denmark is comparable with those in central European countries [69, 70]. The costs for long-term work loss were calculated using SHARE data [68] 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 [71]). Production costs per hour were also obtained from the Eurostat website [72]. See Supplement 2 for more details. Costs for informal care were based on SHARE data [68] 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 Supplement 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

Table 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 [49]
RRs for the co-occurrence of diseases	RR specified by age and sex.	–	Fixed	Different sources [51–53]
RRs for association BMI and all-cause mortality	RR varied by BMI, specified by sex.	–	Normal distribution	Aune et al. [50]
Disease prevalence, incidence, and mortality	On the basis of 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 [49–58]
Discount rate				
Costs	4%	–	–	Ehlers et al. [64]
Effects	4%	–	–	Alban et al. [43]
Population				
Proportion men, %	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. [27]
Effect loss BMI per year, percentage (proportion)	17.9% (0.1786)[b]	+/− 20%	–	Knowler et al. [59]
Duration effect loss BMI, year	5	1–7	–	Assumption based on Knowler et al. [59]
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. [27]
QALY—utility decrements for obesity-related diseases:				
Diabetes	−0.069	–	Fixed	Sullivan et al. & Sørensen et al. [62, 63]
IHD	−0.061	–	Fixed	
Stroke	−0.114	–	Fixed	
Costs 2020 € (DKK)				
Total intervention costs				
PP	7402 (55,277)	+/− 20%	Normal	Trial data
Control	5653 (42,215)	+/− 20%	distribution	Trial data
Duration effect costs (intervention period), years	0.19	–	–	Trial duration, Aldubayan et al. [27]
Treatment of diseases				
Diabetes[c]	6342 (47,363)	+/− 20%	Gamma	Sortsø et al.[67]
IHD first year	19,677 (146,950)	+/− 20%	Gamma	Ehlers et al.[64] & Brorholt et al. [66]

Table 2 (continued)

Parameter	Deterministic value	Sensitivity analysis range (CI 95% or assumption)	Distribution	Source
IHD subsequent year	480 (3585)	+/− 20%	Gamma	Ehlers et al.[64] & Brorholt et al. [66]
Stroke first year	16,300 (121,729)	+/− 20%	Gamma	Ehlers et al.[64] & Jennum et al. [65]
Stroke subsequent year	2896 (21,628)	+/− 20%	Gamma	Ehlers et al.[64] & Jennum et al. [65]
Productivity loss				
Hourly rate	45.3 (338)	+/− 20%	Gamma	Eurostat [72]
Informal care				
Hourly rate	21.0 (157)	+/− 20%	Gamma	Ecorys [81]
Unrelated medical costs	Depending on age and sex (+ divided by 'last year of life' and 'other years of life')	+/− 20%	Gamma	Different sources (see Supplement 3)
Non-medical costs	Depending on age and sex	+/− 20%	Gamma	Different sources [73, 74, 82]

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. [30] for methods regarding the calculation of transition probabilities

[b] Knowler et al. [59] 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 with type 1 [83]

consumption expenditure [73] by taking into account household size [74] and by correcting for the probability of having more than one adult per household [75]. See Supplement 4 for more details.

All costs were converted to 2020 currency using the consumer price index for Denmark [76]. Thereafter, as recommended by the ISPOR's guideline on good research practices [77], the costs were converted to DKK using purchasing power parity (PPP) [78] and exchange rates [79], depending on the source. All costs were then converted from 2020 DKK to 2020 € using exchange rates (1 DKK = 0.134€) [79]. Costs were discounted at 4% annually [43, 44, 64].

2.5.3 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 [64, 80], since no specific threshold value was recommended in the guideline [43, 44].

2.5.4 Sensitivity Analyses

2.5.4.1 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-effective-

ness analyses [84]. We did not include subgroup analyses since heterogeneity was not studied in the trial analyses, mainly because of sample size limitations [27, 85].

2.5.4.2 Probabilistic Sensitivity Analysis Probabilistic sensitivity analysis (PSA) was performed with enough iterations (5000) 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 2). See Supplement 5 for more information on the PSA inputs. Results were presented in a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) [86].

3 Results

3.1 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 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 [27].

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). 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.

When costs of the two interventions were analyzed, a difference in total costs of 1749€ was found (Table 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 1 presents weighted average costs for these ingredients. The costs for the tests represented a one-time expenditure.

3.2 Base-case estimates of lifetime costs and effects

Table 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 1736€ (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 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							
Female	–	–	37 (76)	–	–	32 (63)	0.17
Male	–	–	12 (24)	–	–	19 (37)	
BMI (kg/m^2)	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-value of the means were given; if not, the p-value of the medians were given

Table 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/m^2)	−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

3.3 Univariate Sensitivity Analyses and Scenario Analysis

Results from the univariate sensitivity analyses of different parameters are shown in Fig. 2A–C. The change in intervention costs had the most impact on the incremental costs, followed by the intervention's effect on BMI (see Fig. 2A). The most impactful parameter for the incremental QALYs was the duration of the QoL effect (see Fig. 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 (Fig. 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), 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) 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 Fig. 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 1213€ (9060 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 [1658€ (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 Supplement 6 for detailed results of this scenario analysis.

3.4 Probabilistic Sensitivity Analysis (PSA)

Fig. 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 Fig. 5, in which the cost-effectiveness acceptability curve is shown. Fig. 5 shows that by a WTP threshold of 200,856€ (1,500,000 DKK) the probability of PP being cost-effective is 57%. On the basis of the PSA results, the mean QALY gain from PP is 0.011 (95% CI −0.015, 0.04) and mean cost increase is 1748€ (13,055 DKK) [95% CI 1592€ (11,892 DKK), 1907€ (14,239 DKK)].

4 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 (CI 95% −0.51, 0.38) between the

Table 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 diabetes/1000[a]	377.255	378.201	−0.946	377.255	378.201	−0.946
Cum. Incident cases IHD/1000[a]	279.448	279.788	−0.34	279.448	279.788	−0.34
Cum. Incident cases stroke/1000[a]	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 (−1173)
IHD	2910 (21,732)	2916 (21,774)	−6 (−43)	7219 (53,915)	7230 (53,997)	−11 (−82)
Stroke	3642 (27,199)	3649 (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 (1684)
Intervention[a]	7402 (55,277)	5653 (42,215)	1749 (13,062)	7402 (55,277)	5653 (42,215)	1749 (13,062)
Informal care	5581 (41,680)	5582 (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)	1736 (12,963)	1,102,555 (8,233,918)	1,100,663 (8,219,788)	1892 (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

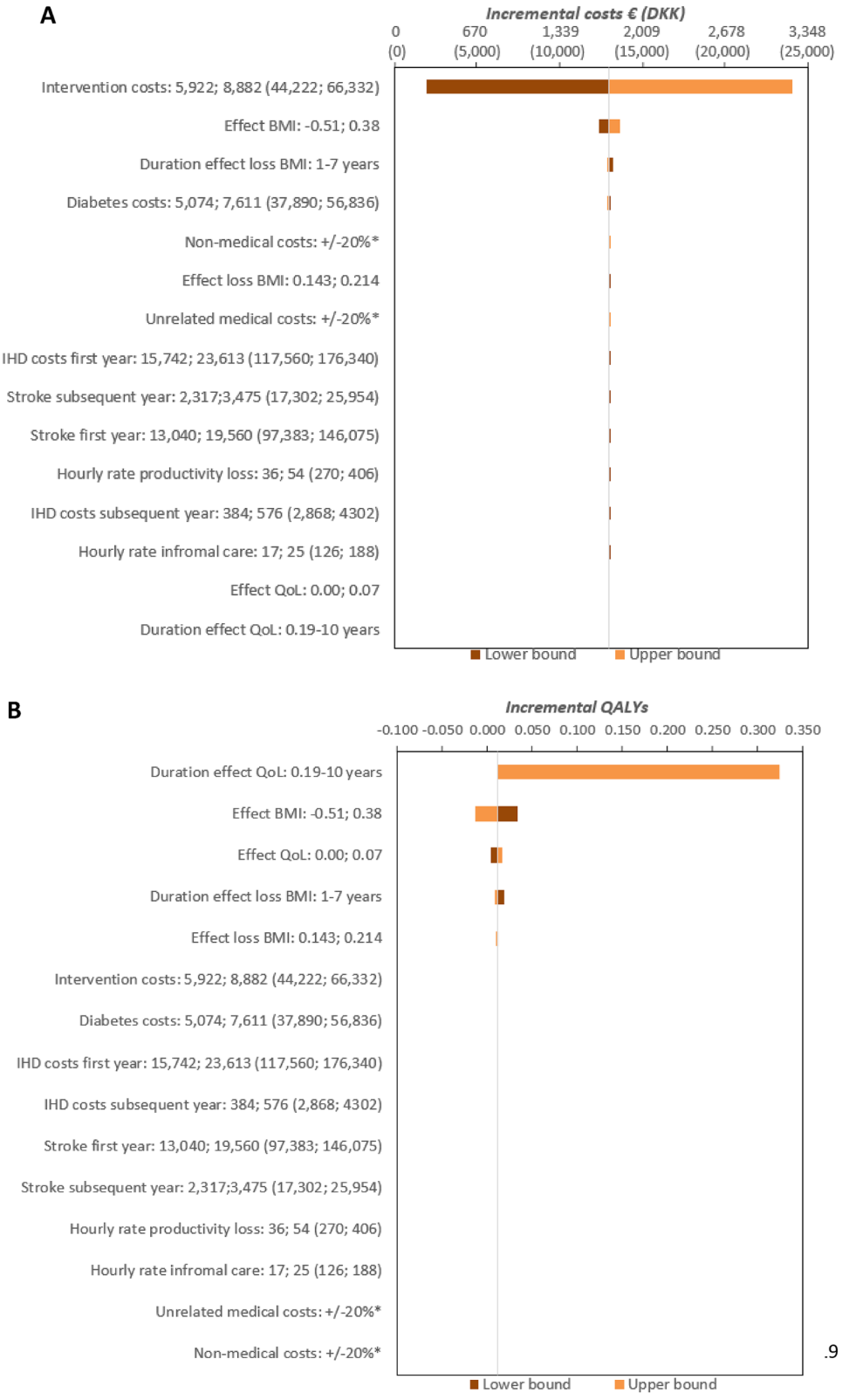
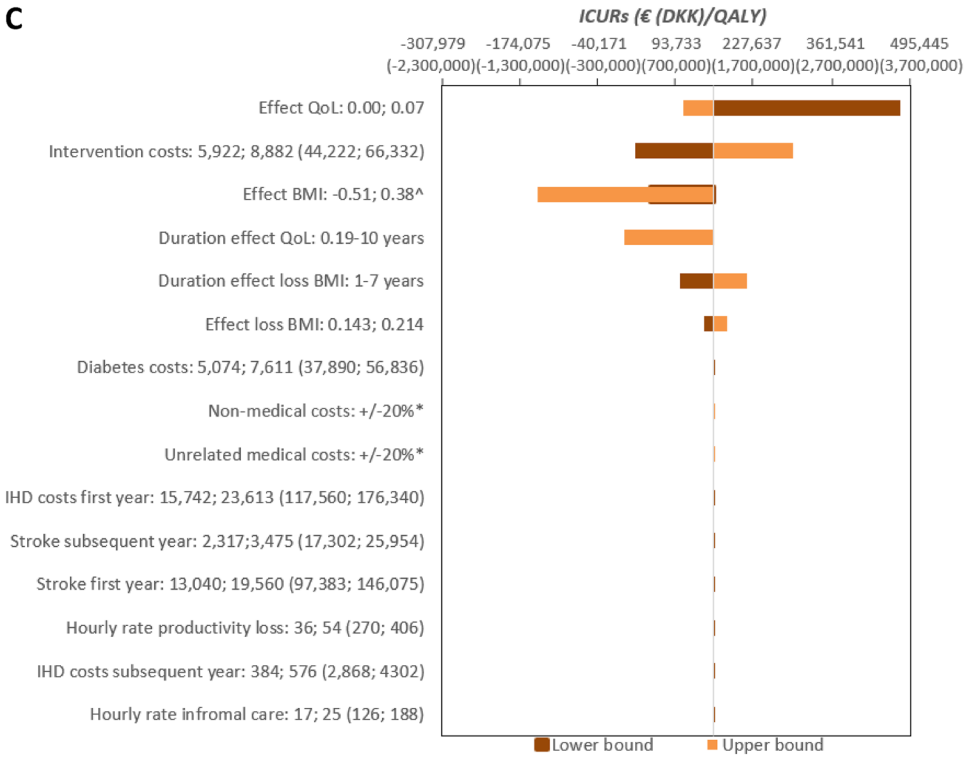


Fig. 2 Tornado diagrams for change in incremental costs in € (DKK) (**A**), incremental QALYs (**B**), and ICUR (**C**) using lower and upper bounds of parameters. *BMI* body mass index, *DKK* Danish krone, *ICUR* incremental cost-utility ratio, *IHD* ischemic heart disease, *QALYs* quality-adjusted 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)

.9

Fig. 2 (continued)



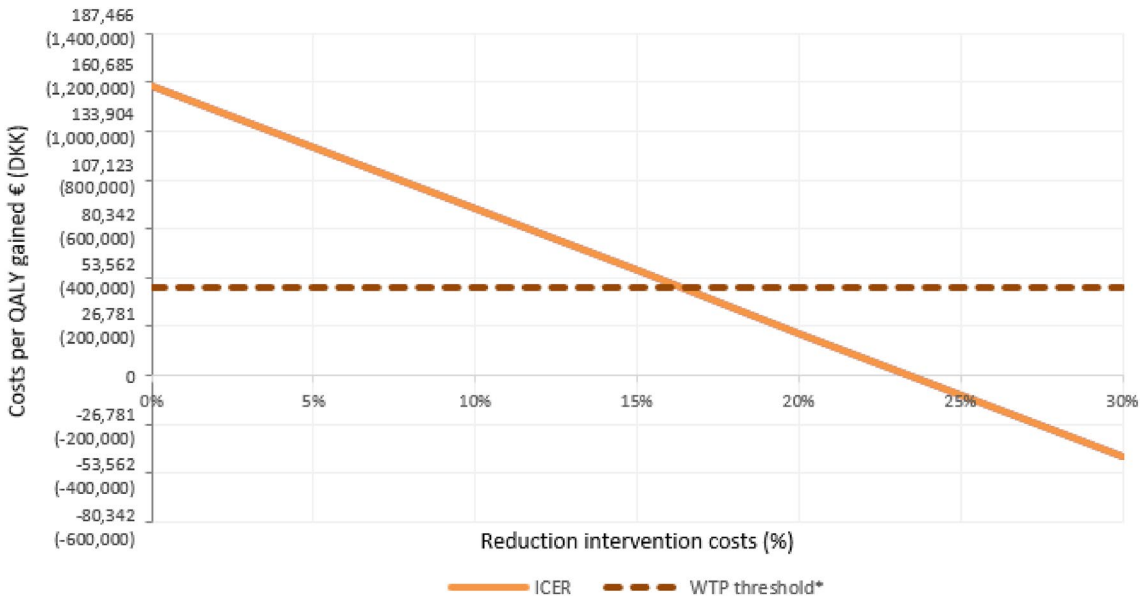


Fig. 3 Influence of reduction in intervention costs on cost-effectiveness. *QALYs* quality-adjusted life years, *DKK* Danish krone, *ICUR* incremental cost-utility ratio, *WTP* willingness-to-pay. *WTP threshold = 357,100 DKK per QALY gained (47,817€)

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 [1736€ (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).

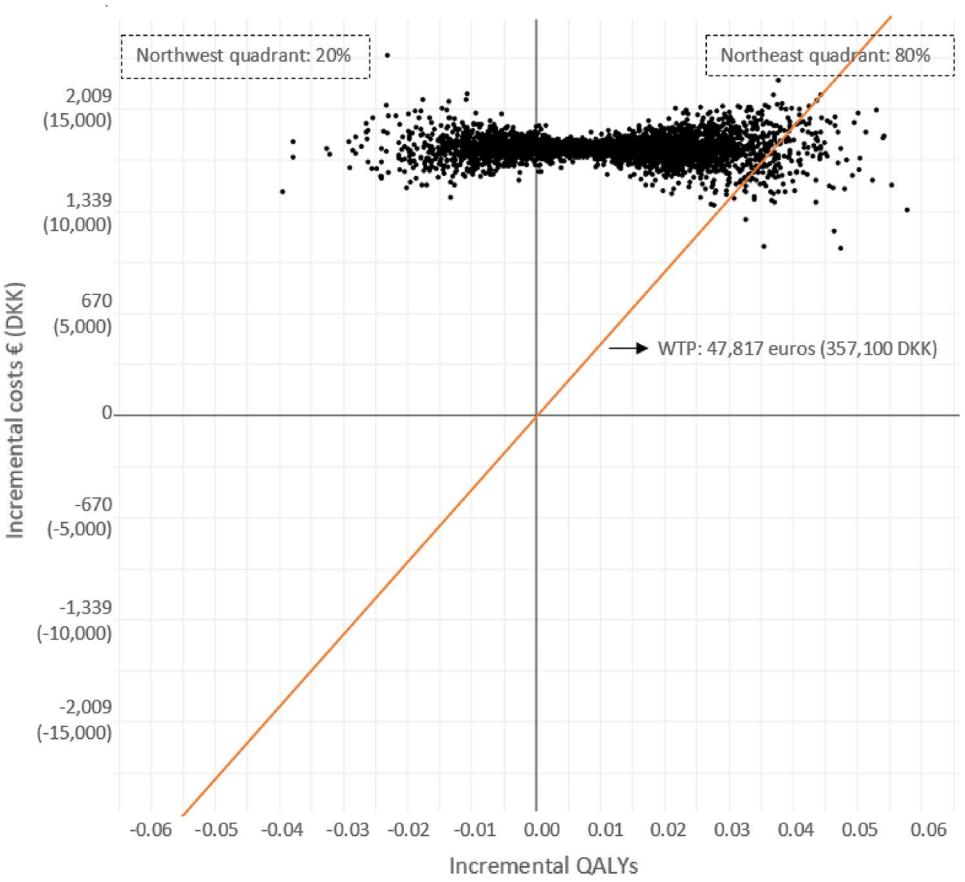


Fig. 4 Probabilistic sensitivity analysis of the cost-effectiveness of PP versus control. *QALYs* quality-adjusted life years, *DKK* Danish krone, *PP* personalized plan, *WTP* willingness to pay

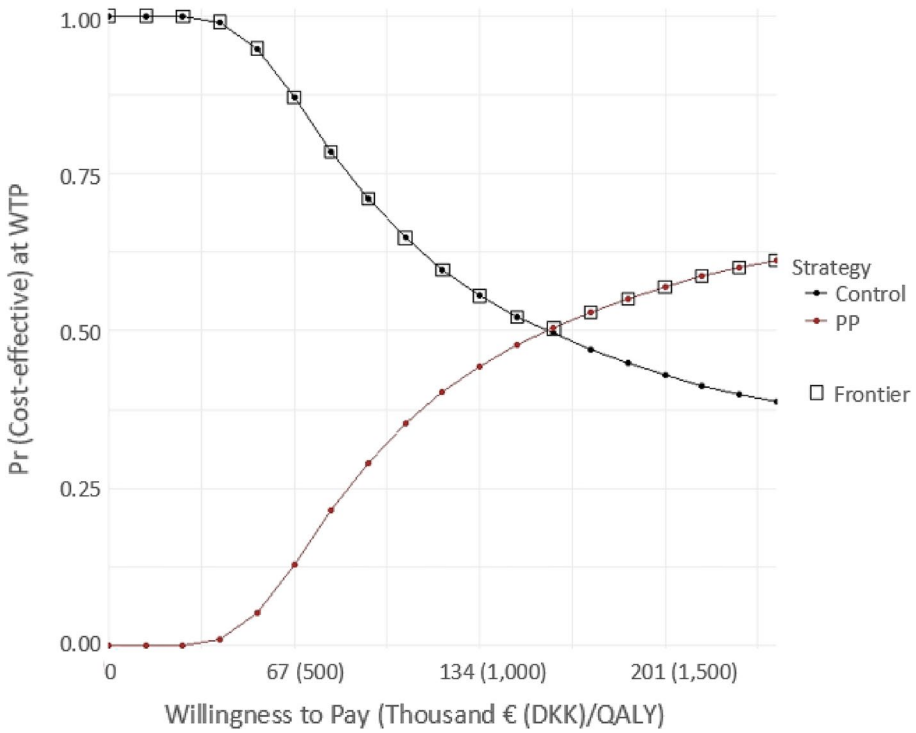


Fig. 5 Cost-effectiveness acceptability curve plot. *DKK* Danish krone, *PP* personalized plan, *Pr* probability, *QALY* quality-adjusted life year, *WTP* willingness to pay

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 [19]. 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 [28]. 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 −2000 (−1886€) and +2000 dollars (+1886€)] compared with the incremental costs in our study (+1736€). The lack of studies exploring personalized nutrition interventions on the basis of omics science, which incurs higher costs [29], 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 [87, 88] and vitamin or protein intake [89, 90]. 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 [28, 91–94]. 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 [95]. For example, body fat might be a better measure for 'weight loss' since it is the most metabolically harmful tissue type [1, 96]. 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 [30]. This model used BMI as a continuous parameter, unlike most previously published obesity models that include classes (e.g., normal weight, overweight, and obese) [97]. 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 [98]. Third, studies have shown that there is a strong correlation between body fat and BMI [99], which was also found in the Danish trial results [27]; 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 [28]. 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 [92]. 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 [100]. 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 [76]. 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 [21]. 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 [101]. 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, on the basis of the literature [59], 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 [102]. 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) [103–105], 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 [106]. Moreover, this research could be extended to other countries as well to see if similar cost-effectiveness results are found [30].

We found that PP would not be considered cost-effective on the basis of 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.

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Declarations

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Conflict of Interest MMJG, CUG, and WKR declare that they have no conflict of interest.

Availability of Data and Material The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MMJG and WKR. The first draft of the manuscript was written by MMJG and all authors (MMJG, WKR, and CUG) commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability (software application or custom code) This code is available upon reasonable request.

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