ScienceDirect
Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

A Systematic Review of Cost-Effectiveness Studies of Interventions with a Personalized Nutrition Component in Adults

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

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-four 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-eight CEAs (49%) 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.

Keywords: nutrition, personalized, cost-effectiveness, systematic review.

VALUE HEALTH. 2021; ■(■):■–■

Introduction

There are well-established links between poor dietary patterns, representing a complex set of highly correlated dietary exposures[1] and an increased risk of different diseases.[2,3] Obesity may be an intermediate outcome of these links,[4] since obesity often leads to diet-related diseases such as type 2 diabetes, heart disease, stroke, and cancer.[2] In other cases, poor dietary patterns can arise from other problems (eg, hip fracture), which may lead to malnutrition and possibly result in disorders such as functional disability and impaired cognitive function.[5] 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.[6] 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 (ie, population level), they often have poor individual-level effectiveness.[3,7] Studies have shown this might be caused by inter-individual variability of metabolic responses to specific diets and food components that affect health.[8,9] Knowledge about an individual's response could lead to a personalized intervention to maximize the potential health benefits of these diets and food components.[9]

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,[2] 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.[10] However, policy decisions must be guided by their ability to improve health outcomes and their cost-effectiveness,[11] given the ever-present tension between effectiveness and financial constraints.[12] In fact, various cost-effectiveness analyses (CEAs) of nutrition interventions have been published, and systematic reviews of these CEAs have been conducted.[11,13,14] However, these reviews often focused on specific diseases or interventions (eg, salt reduction[14]). 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.[2,12] 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.[12,15,16] 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 (ie, Embase, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google Scholar). Search terms (including MESH terms and text words) were terms related to CEA (eg, economic evaluation), nutrition (eg, diet therapy), and personalization (eg, individual). Specific search queries are provided in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006.

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 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 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).[17,18] 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 (eg, intervention characteristics including definitions) were collected as well as economic findings themselves (eg, 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 (ie, biomarkers, genotype, and microbiota) ("biological concept").[2,19]

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[20] and converted to Unites States dollars (US$) using the purchasing power parity.[21] If the cost year of the study was not specified, it was assumed to be the year of publication. To determine whether an intervention would be considered cost-effective, ICURs were compared with 2 willingness-to-pay (WTP) thresholds (values in US$ per quality-adjusted life-years (QALY)): $20 000 (close to the thresholds of £20 000 ($25 937[22]) used in United Kingdom and €20 000 ($23 680[22]) in The Netherlands for interventions targeting diseases with a low disease burden[23]) 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 (ie, population, intervention, choice of comparator) and modeling choices (ie, 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,[24] which is preferred when modeling studies are included.[16] This checklist consists of 24 items, subdivided into 6 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

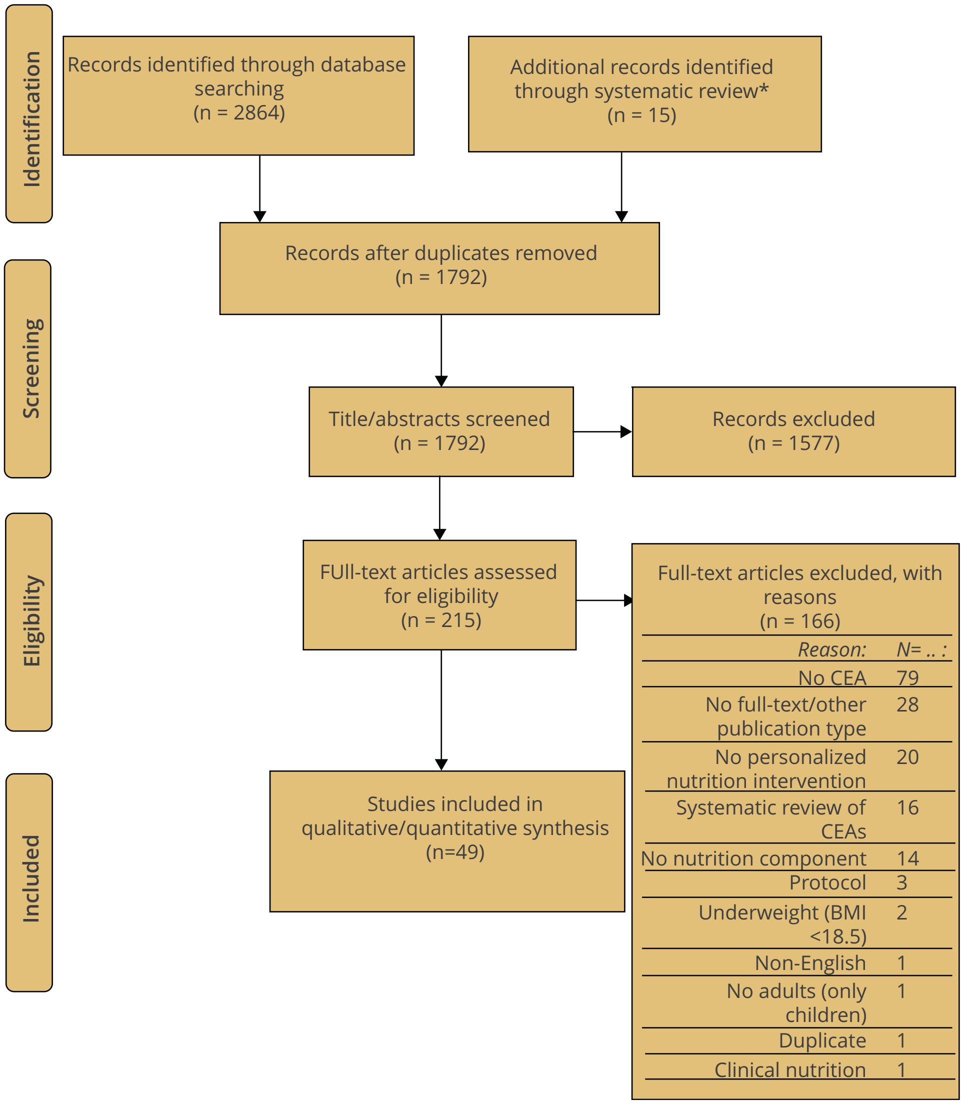
The database searches identified 2864 articles (Fig. 1[25]); an additional 15 records[26–40] were identified manually via systematic reviews.[41–46] After removing duplicates, 1792 records were screened on title/abstract, and 1577 records were excluded based on the eligibility criteria. The remaining 215 articles underwent full-text screening, which resulted in a final list of 49 articles. Most studies were performed in Europe (44% (n = 24)[31–33,35,36,38,41,47–63]), of which 10 studies were in the UK.[33,35,41,49,53,55,56,58,59,61] Almost as many were performed in North America (n = 22 (42%)[26,28,30,34,39,40,64–79]). Dalziel et al[80] conducted different CEAs, of which we included 5,[56,63,68,81,82] 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.

Population and Intervention

Figure 2 provides an overview of the general study characteristics (ie, populations, interventions, methods); Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 provides detailed information per study. Nine studies focused on interventions related to the Diabetes Prevention Program (DPP)[26,28–30,39,40,45,50,71] and 4 on the Diabetes Prevention Study (DPS).[31,32,36,41,80] 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.[83] DPS was a Finnish randomized controlled trial with a personalized lifestyle intervention arm.[84,85]

Fifteen CEAs[27,33,34,37,38,61,64,69,73,75,76,78–80] focused on the obesity/diabetes/impaired glucose tolerance population but studied interventions other than DPP/DPS (Fig. 2, Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006). These interventions were mostly computer-based (n = 6

Figure 1. PRISMA diagram.



CEA indicates cost-effectiveness analysis. *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.

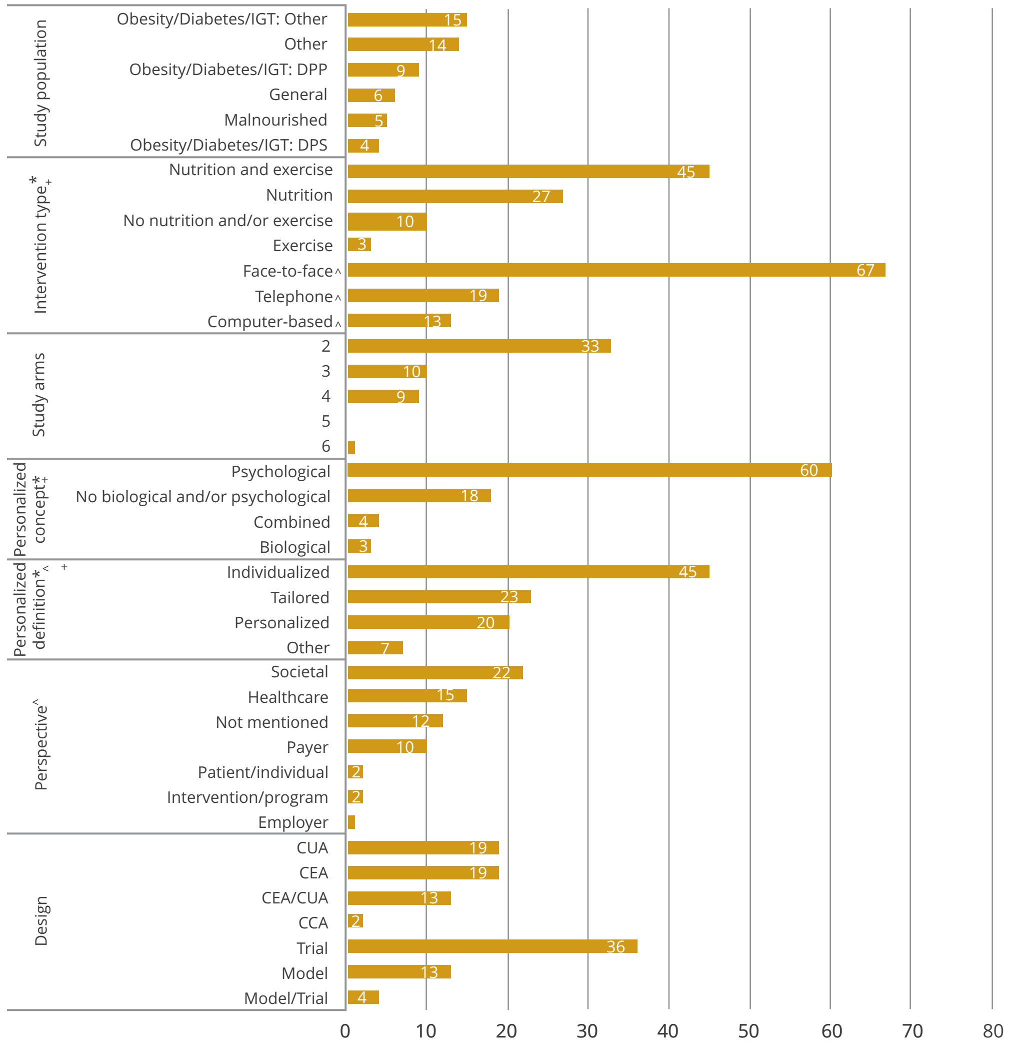
studies; 7 arms[33,34,37,73,75,79]) and comprised interventions with only a nutrition component[27,37,61,78,79,81] instead of exercise and nutrition as in DPP/DPS. Other CEAs focused on general/healthy populations (n = 6[31,54,67,72,80]) or "other" populations such as depression (n = 14[47–49,53,55,57–59,62,65,70,74,77,86]). The only CEA in the review that assessed an intervention based on only the biological concept of PN was found here.[47] CEAs found in malnourished (at risk of undernutrition) populations (n = 5[51,52,60,87,88]) 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[60,87] as well as CEAs of other populations.[78,82]

In total, 34 studies had 1 or more arms that defined PN as "individualized" nutrition (arms: 46%, n = 45), followed by 18 studies[28,36,39–41,45,47,48,50,54,56,58,60,63,72,75,77,84] that used "tailored" (arms: 23%, n = 23) and 18 studies[33,48,49,52–56,58,61,62,67,68,72,73,77,81,86] that used "personalized" (arms: 19%, n = 20) (Fig. 2, Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006). Ordovas et al[2] 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[47] (n = 3 arms) applied personalization based on the biological concept, and 4 studies[59,68,78,88] (n = 4 arms; 1 arm per study) used interventions that comprised both concepts (integrated approach).

Methodology of the CEAs

Nineteen studies[27,28,30,32,33,39,41,47–49,55,57–59,61,71,74,86,87] involved a CUA and reported QALYs as outcome measure; 13 studies[26,31,36,52,54,56,60,62,63,65,68,81,88] conducted both a CEA and CUA. Other studies conducted a CEA (n = 19[29,34,37,38,40,45,50,53,64,67,70,72,73,75–79,82]) and cost-consequence analysis (CCA) (n = 2[51,69]); these studies used other outcome measures such as weight change (n = 10[34,51,52,60,63,64,76,81,82,89])

Figure 2. Frequencies regarding study design elements.



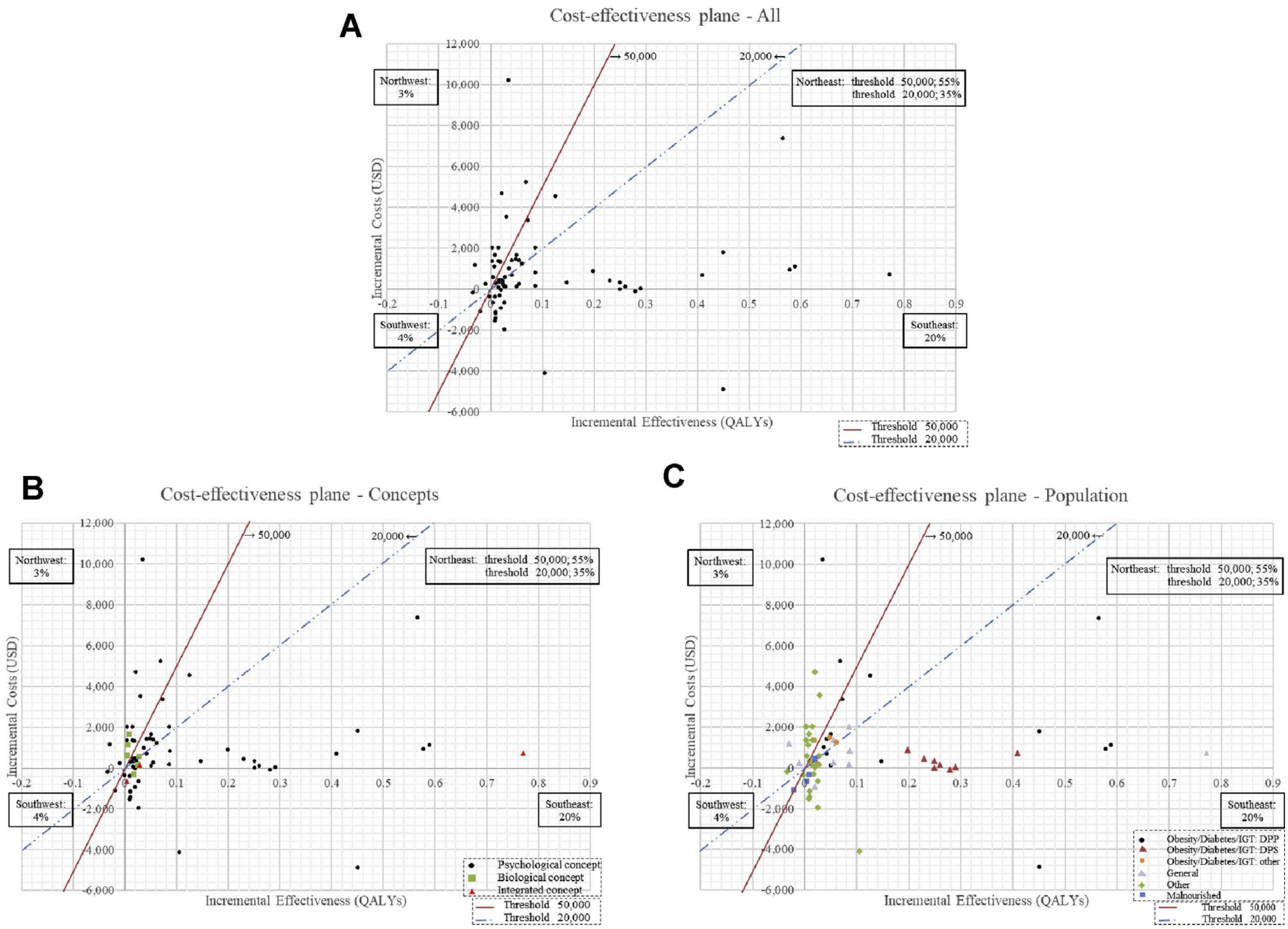
CBA indicates cost-benefit analysis; CCA, cost-consequences analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; IGT, impaired glucose tolerance. Study design elements are shown on the y-axis and frequencies are shown 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.

and life-years gained (n = 6[31,36–38,40,45]) (Fig. 2, Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006). Two CUAs also calculated the iNMB using WTP thresholds not specifically related to nutrition interventions.[54,74] Most studies (n = 36) were trial-based, 13 were model-based,[28,30–32,36,37,39–41,45,47,50,71] and 4 studies used both.[56,63,68,81] The range of time horizons among the trial-based studies was 0.08 years (4 weeks)[53] to 6 years,[48,63] whereas the range of time horizons in the model-based studies was 3 years[50] to lifetime.[30,31,36,39,45,47] See Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 for frequencies of time horizons.

The societal perspective was most commonly used (n = 22[26,28,30–33,36,49,50,52,54,56,58,60,63,65,68,71,74,81,82,86]), followed by healthcare (n = 15[26,29,30,48,49,55,57,61,62,71,78,79,86–88]) and payer (n = 10[28,31,39–41,45,47,50,73,75]); other CEAs used a patient perspective (n = 2[28,76]), intervention/program (n = 2[76,77]), and employer (n = 1[65]) (Fig. 2, Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006). Most studies used "usual care" or "standard care" as comparator. However, some studies used other comparators; Herman et al[30] used metformin, and Sukhanova et al[72] 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) (Fig. 2, Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006). However, in some CUAs subgroup analyses were done (eg, overweight, borderline, and obese)[36] and variation in comparators was observed; drug comparators,[26,30] general lifestyle recommendations, or no intervention were used.[28,32,36,39,41,71,80] Moreover, variation was found in the CUA models (ie, different assumptions and approaches). First, time horizons varying from 3 years[26] to lifetime[30,36,39] and societal,[26,28,30,32,36,71,80] payer,[39,41] and health system[26,30,71] perspectives were used. Second, CUAs of the DPS intervention were

Figure 3. Cost-effectiveness plane.



ICURs indicates incremental cost-utility ratios; QALYs, Quality-Adjusted Life Years; USD; United States dollar. Incremental costs (in 2019 USD) are shown 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 3A provides the ICURs of all studies, Figure 3B shows the ICURs arranged according to the concepts of personalized nutrition used in the studies, and Figure 3C shows the ICURs according to the population that was studied.

done with Markov models using 3,[41] 4,[36,80] or 7[32] 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[36] through CVD risk factors alone,[32] or no CVD risk factors were modeled.[41] Third, models in DPP interventions varied; 4[39,71] or 5[30] health states were used in Markov models, and Eddy et al[28] used the Archimedes model (addresses what happens underneath clinical states, between annual jumps and inside transition probabilities). See Appendices 3 and 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 for detailed information about modeling approaches in DPP/DPS studies.

Results of the CEAs

Appendix 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 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[80] to 0.77[68] was found. The smallest QALY gain was seen in the malnourished population (maximum:0.020 QALYs[87]), 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[33,49,50,57,62,64,76]) concluded that the intervention was not cost-effective, 11% considered the intervention cost-effective in some subgroups (sometimes) (n = 6[47,48,52,54,60,74]), and 30% (n = 17[27,28,34,39,41,51,55,58,59,67,73,75,80]) had no conclusion.

Figure 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 3A leads to a range in iNMB (λ = 50 000) of $-8531[28] to $37 862[68] (mean: $4456). Table 1 provides results of the additional analyses with the iNMB. Appendix 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 provides all (converted) costs/ICURs.

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[48] to 0.7714[68] and costs varying from $-4877[30] to $7369[30] (iNMB(λ = $50 000) mean: $5769) (Table 1). In contrast, interventions considered not cost-effective by the authors showed incremental QALYs varying from -0.0340[48] to 0.0200[54] and costs from $-1087[60] to $2026[49] (iNMB(λ = $50 000) mean: $-940).

Second, variation in incremental costs, QALYs, and iNMB is seen between the PN concepts (Fig. 3B). The highest mean iNMB (λ = $50 000) was found in the integrated approach ($13 366), followed by the psychological concept ($4443) and the biological concept ($13) (Table 1). Third, a wide variation in incremental costs and QALYs is found within the DPP and DPS interventions, despite their comparable PICOs (Fig. 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) $-8531),[28] and the other outlier reported costs of $-4877 and QALY gain of 0.4500 (iNMB (λ = $50 000) $27 377).[30]

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 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006); slightly different populations were studied in different countries (eg, Switzerland[36] and the UK[41]). 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[80] (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.[41] See Appendix 5 for information about modeling approaches of DPP/DPS studies and Appendix 8 for the cost-effectiveness planes divided by different characteristics of DPP/DPS interventions (Appendices 5 and 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006).

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[30] and Eddy et al.[28] These differences might be explained by different assumptions. First, Herman et al[30] used a 70-year time horizon and studied 1 intervention over time, whereas Eddy et al[28] 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[28] did not assume a constant transition rate, resulting in less cost-savings than Herman et al.[30] Third, Eddy et al[28] incorporated a considerably higher level of biological detail and clinical realism, which affected the outcomes.

Quality of Economic Analyses

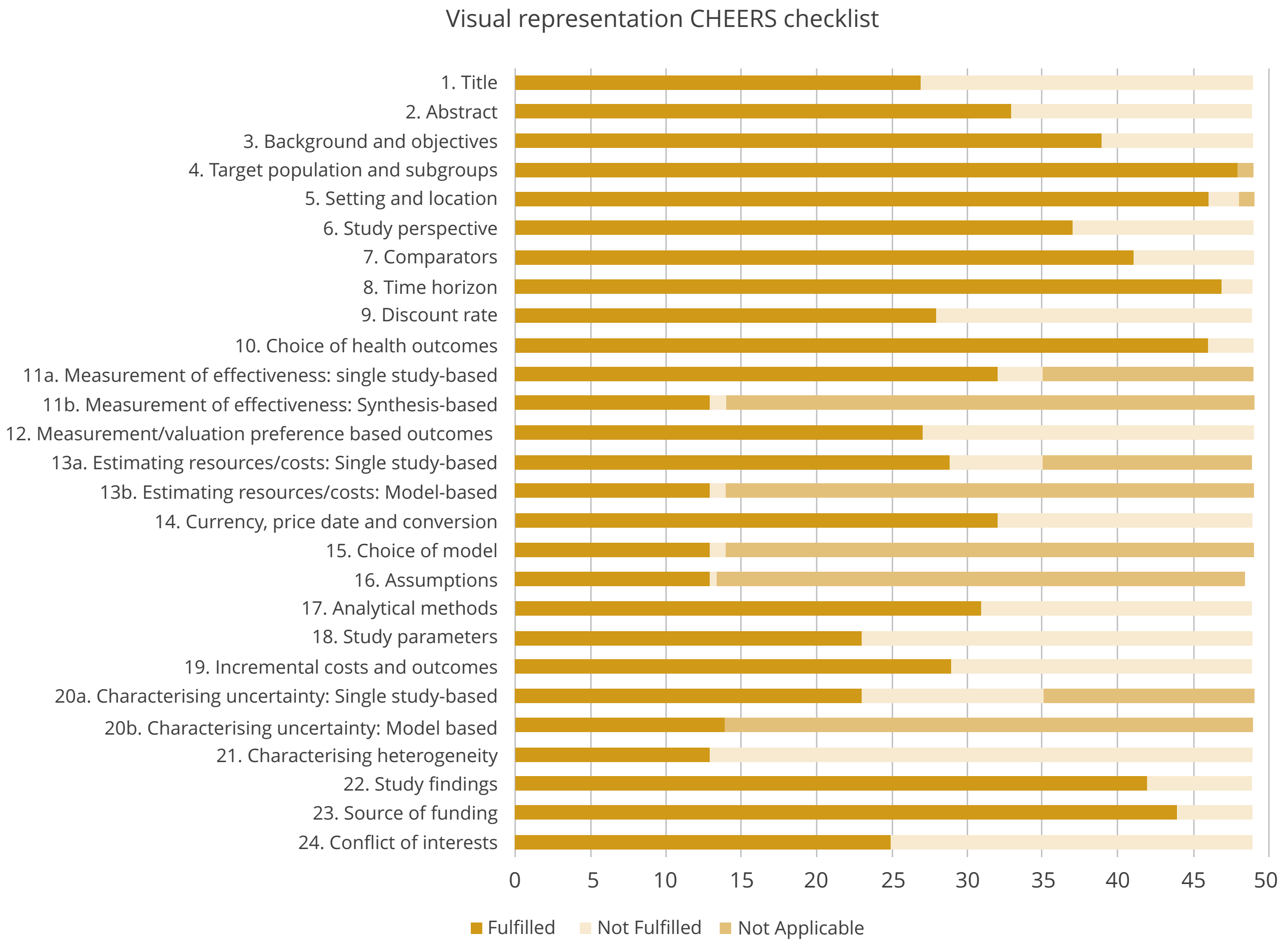
Figure 4 summarizes the quality of reporting using the CHEERS checklist.[24] Many studies showed a high quality of reporting their results, but 6 studies[53,59,67,69,70,89] reported 10 or fewer statements

Table 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)	Lowest value in $ (WTP $20 000)	Highest value in $ (WTP $20 000)	Mean in $ (WTP 20 000)	Number of iNMB values
iNMB categorized by population							
Obesity/diabetes/IGT population: DPP	−8531	28 300	9212	−9557	13 877	2227	14
Obesity/diabetes/IGT population: DPS	793	14 461	11 852	−293	7481	4509	9
Obesity/diabetes/IGT population: Other	−433	1794	818	−980	263	−315	4
General	−2677	37 862	4026	−1777	14 715	1266	13
Other	−3657	9357	556	−4280	6207	60	25
Malnourished	87	900	581	−61	750	480	4
Total	**−8531**	**37 862**	**4456**	**−9557**	**14 715**	**1310**	**69**
iNMB categorized by authors' conclusion about cost-effectiveness							
Cost-effective (yes) or sometimes (cost-effective answer)	−2053	37 862	6169	−3880	14 715	2188	47
Not cost-effective (no) or sometimes (not cost-effective answer)	−3657	268	−940	−4280	687	−979	15
iNMB categorized by concept							
Biological concept	−1226	1215	135	−1485	673	-323	6
Psychological concept	−8531	28 300	4443	−9557	13 877	1273	60
Combination of concepts	900	37 862	13 366	449	14 715	5305	3

DPP indicates Diabetes Prevention Program; DPS, Diabetes Prevention Study; IGT, impaired glucose tolerance; iNMB, incremental net monetary benefit; WTP, willingness-to-pay.

Figure 4. Study quality based on the CHEERS checklist. CHEERS indicates 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 (ie, 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.



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[28,30,48,60,78,31,34–39,47] reported this appropriately. Appendix 9 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.12.006 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[47] on the biological concept and 4 studies[59,68,78,88] on the integrated approach. Approximately half of the authors concluded that an intervention with a PN component was cost-effective (49%). 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[34] used “individualized” to describe individual counseling sessions with goal-setting and individual feedback, whereas Olsen et al[38] 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,[53] whereas participants receiving a different intervention received personalized messages via the internet when needed.[33] 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 to see not only 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,[28,76] 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[90] 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.[80,91] Furthermore, nutrition often has a preventive effect, in which benefits take longer timespans to develop.[92] 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) – £5825 ($12 215) (year 15)).[41] 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,[92] and yet there is no systematic approach to assess the health impact of (personalized) nutrition.[93] Therefore, there is still much variation in models for PN (even those with comparable PICOs, eg, 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.[92] For example, Eddy et al[28] 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.[94]

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.[2,19,95] An example of an intervention with an effective integrated approach is Food4Me, which has shown greater improvement in dietary behavior.[10,96] 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.[97] 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.[98] 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.[54] A study by Corso et al[99] 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.[100]

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.[42,101–103] 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.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.12.006.

Article and Author Information

Accepted for Publication: December 19, 2020

Published Online: Month xx, xxxx

doi: https://doi.org/10.1016/j.jval.2020.12.006

Author Affiliation: Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands (Galekop,Uyl-de Groot,Ken Redekop).

Correspondence: Milanne M.J. Galekop, Burgemeester Oudlaan 50, 3062 PA Rotterdam, The Netherlands. Email: galekop@eshpm.eur.nl

Author Contributions: *Concept and design*: Galekop, Uyl-de Groot, Redekop
Analysis and interpretations of data: Galekop, Redekop
Drafting of the manuscript: Galekop, Redekop
Critical revision of the paper for important intellectual content: Galekop, Uyl-de Groot, Redekop
Obtaining funding: Redekop
Administrative, technical or logistic support: Galekop
Supervision: Uyl-de Groot, Redekop

Conflict of Interest Disclosures: Drs Galekop, Uyl-de Groot, and Redekop reported receiving grants from the European Union's Horizon 2020 research and innovation program during the conduct of the study.

Funding/Support: This work was supported by grant No.818318 from the European Union's Horizon 2020 Union's Horizon 2020 research and innovation program (project named PREVENTOMICS).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: The authors would like to acknowledge Wichor M. Bramer who helped with the design of the systematic literature search strategy.

REFERENCES

1. Cutler GJ, Flood A, Hannan PJ, Slavin JL, Neumark-Sztainer D. Association between major patterns of dietary intake and weight status in adolescents. *Br J Nutr*. 2012;108(2):349–356.
2. Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. *BMJ*. 2018;361:1–7.
3. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol*. 2014;2(1):56–64.
4. WHO. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed December 2, 2019.
5. Wyers CE, Reijven PLM, Breedveld-Peters JJL, et al. Efficacy of nutritional intervention in elderly after hip fracture: a multicenter randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2018;73(10):1429–1437.
6. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: a systematic literature review. *Int J Environ Res Public Health*. 2017;14(4):1–18.
7. Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. *Lancet Diabetes Endocrinol*. 2018;6(5):416–426.
8. de Toro-Martín J, Arsenault BJ, Després JP, Vohl MC. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients*. 2017;9(8):1–28.
9. Ohlhorst SD, Russell R, Bier D, et al. Nutrition research to affect food and a healthy lifespan. *Am Soc Nutr*. 2013;4:579–584.
10. Celis-Morales C, Livingstone KM, Marsaux CFM, et al. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. *Int J Epidemiol*. 2017;46(2):578–588.
11. van Dongen JM, Proper KI, van Wier MF, et al. A systematic review of the cost-effectiveness of worksite physical activity and/or nutrition progra. *Scand J Work Environ Heal*. 2012;38(5):393–408.
12. van Mastrigt GAPG, Hiligsmann M, Arts JJC, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). *Expert Rev Pharmacoeconomics Outcomes Res*. 2016;16(6):689–704.
13. Alouki K, Delisle H, Bermúdez-Tamayo C, Johri M. Lifestyle interventions to prevent type 2 diabetes: a systematic review of economic evaluation studies. *J Diabetes Res*. 2016;2016:1–14.
14. Schorling E, Niebuhr D, Kroke A. Cost-effectiveness of salt reduction to prevent hypertension and CVD: a systematic review. *Public Health Nutr*. 2017;20(11):1993–2003.
15. Thielen FW, Van Mastrigt GAPG, Burgers LT, et al. How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev Pharmacoeconomics Outcomes Res*. 2016;16(6):705–721.
16. Wijnen B, Van Mastrigt G, Redekop W, Majoie H, De Kinderen R, Evers SMAA. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). *Expert Rev Pharmacoeconomics Outcomes Res*. 2016;16(6):723–732.
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159.
18. Wikipedia. Cohen's kappa. https://en.wikipedia.org/wiki/Cohen%27s_kappa. Accessed May 6, 2020.
19. Biesiekierski JR, Livingstone KM, Moschonis G. Personalised nutrition: updates, gaps and next steps. *Nutrients*. 2019;11(8):10–14.
20. Organisation for Economic Co-operation and Development. Inflation (CPI) (indicator). https://doi.org/10.1787/eee82e6e-en. Accessed April 2, 2020.
21. Organisation for Economic Co-operation and Development. PPPs and exchange rates. https://stats.oecd.org/Index.aspx?DataSetCode=SNA_TABLE4. Accessed April 2, 2020.
22. XE Currency Converter. USD-US dollar. https://www.xe.com/currency/usd-us-dollar. Accessed September 15, 2020.
23. Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-Effectivenss in Practice (Kosteneffectiviteit in de Praktijk); 2015. https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/document en/publicaties/rapporten-en-standpunten/2015/1506-kosteneffectiviteit-in-de-praktijk/Kosteneffectiviteit+in+de+praktijk.pdf.
24. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013;346:1–6.
25. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7).
26. The Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26(9):2518–2523.
27. Kaplan RM, Atkins CJ, Wilson DK. The cost-utility of diet and exercise interventions in non-insulin-dependent diabetes mellitus. *Health Promot Int*. 1987;2(4):331–340.
28. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med*. 2005;143(4).
29. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care*. 2007;30(10):2548–2552.
30. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med*. 2005;142(5):323–332.
31. Lindgren P, Fahlstadius P, Hellenius ML, Jönsson B, De Faire U. Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm: a stochastic model of exercise and dietary advice. *Prev Med (Baltim)*. 2003;36(4):403–409.
32. Lindgren P, Lindström J, Tuomilehto J, et al. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. *Int J Technol Assess Health Care*. 2007;23(2):177–183.
33. McConnon Á, Kirk SFL, Cockroft JE, et al. The Internet for weight control in an obese sample: results of a randomised controlled trial. *BMC Health Serv Res*. 2007;7:1–9.
34. Sherwood NE, Jeffery RW, Pronk NP, et al. Mail and phone interventions for weight loss in a managed-care setting: Weigh-to-be 2-year outcomes. *Int J Obes*. 2006;30(10):1565–1573.
35. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clin Ther*. 2004;26(2):304–321.
36. Galani C, Schneider H, Rutten FFH. Modelling the lifetime costs and health effects of lifestyle intervention in the prevention and treatment of obesity in Switzerland. *Int J Public Health*. 2007;52(6):372–382.
37. Segal L, Dalton AC, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promot Int*. 1998;13(3):197–209.
38. Olsen J, Willaing I, Ladelund S, Jørgensen T, Gundgaard J, Sørensen J. Cost-effectiveness of nutritional counseling for obese patients and patients at risk

of ischemic heart disease. *Int J Technol Assess Health Care*. 2005;21(2):194–202.
39. Ackermann RT, Marrero DG, Hicks KA, et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. *Diabetes Care*. 2006;29(6):1237–1241.
40. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. *Diabet Med*. 2004;21(11):1229–1236.
41. Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess (Rockv)*. 2004;8(21):3–7.
42. Boyers D, Avenell A, Stewart F, et al. A systematic review of the cost-effectiveness of non-surgical obesity interventions in men. *Obes Res Clin Pract*. 2015;9(4):310–327.
43. Robertson C, Archibald D, Avenell A, et al. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. *Health Technol Assess (Rockv)*. 2014;18(35):1–424.
44. Flodgren G, Gonçalves-Bradley DC, Summerbell CD. Interventions to change the behaviour of health professionals and the organisation of care to promote weight reduction in children and adults with overweight or obesity. *Cochrane Database Syst Rev*. 2017;2017(11).
45. Palmer AJ, Valentine WJ, Ray JA. Cost-effectiveness studies of diabetes prevention in high-risk patients. *Expert Rev Pharmacoeconomics Outcomes Res*. 2004;4(4):393–402.
46. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. *Int J Environ Res Public Health*. 2010;7(8):3150–3195.
47. Ethgen O, Hiligsmann M, Burlet N, Reginster JY. Cost-effectiveness of personalized supplementation with vitamin D-rich dairy products in the prevention of osteoporotic fractures. *Osteoporos Int*. 2016;27(1):301–308.
48. Gillespie P, Murphy E, Smith SM, Cupples ME, Byrne M, Murphy AW. Long-term cost effectiveness of cardiac secondary prevention in primary care in the Republic of Ireland and Northern Ireland. *Eur J Heal Econ*. 2017;18(3):321–335.
49. Holt RIG, Hind D, Gossage-Worrall R, et al. Structured lifestyle education to support weight loss for people with schizophrenia, schizoaffective disorder and first episode psychosis: the STEPWISE RCT. *Health Technol Assess (Rockv)*. 2018;22(65):1–160.
50. Icks A, Rathmann W, Haastert B, et al. Clinical and cost-effectiveness of primary prevention of type 2 diabetes in a "real world" routine healthcare setting: model based on the KORA Survey 2000. *Diabet Med*. 2007;24(5):473–480.
51. Lorefält B, Andersson A, Wirehn AB, Wilhelmsson S. Nutritional status and health care costs for the elderly living in municipal residential homes: an intervention study. *J Nutr Heal Aging*. 2011;15(2):92–97.
52. van der Pols-Vijlbrief R, Wijnhoven HAH, Bosmans JE, Twisk JWR, Visser M. Targeting the underlying causes of undernutrition. Cost-effectiveness of a multifactorial personalized intervention in community-dwelling older adults: a randomized controlled trial. *Clin Nutr*. 2017;36(6):1498–1508.
53. Price RJG, McMurdo MET, Anderson AS. A personalized snack-based intervention for hip fracture patients: development, feasibility and acceptability. *J Hum Nutr Diet*. 2006;19(2):139–145.
54. Schulz DN, Smit ES, Stanczyk NE, Kremers SPJ, De Vries H, Evers SMAA. Economic evaluation of a web-based tailored lifestyle intervention for adults: findings regarding cost-effectiveness and cost-utility from a randomized controlled trial. *J Med Internet Res*. 2014;16(3).
55. Speed C, Heaven B, Adamson A, et al. LIFELAX - diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people: randomised controlled trial. *Health Technol Assess (Rockv)*. 2010;14(52):1–105.
56. Steptoe A, Perkins-Porras L, McKay C, Rink E, Hilton S, Cappuccio FP. Behavioural counselling to increase consumption of fruit and vegetables in low income adults: randomised trial. *Br Med J*. 2003;326(7394):855–858.
57. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *JAMA Intern Med*. 2015;175(6):901–910.
58. Walters K, Frost R, Kharicha K, et al. Home-based health promotion for older people with mild frailty: the homehealth intervention development and feasibility RCT. *Health Technol Assess (Rockv)*. 2017;21(73):1–127.
59. Whigham L, Joyce T, Harper G, et al. Clinical effectiveness and economic costs of group versus one-to-one education for short-chain fermentable carbohydrate restriction (low FODMAP diet) in the management of irritable bowel syndrome. *J Hum Nutr Diet*. 2015;28(6):687–696.
60. Wyers CE, Reijven PLM, Evers SMAA, et al. Cost-effectiveness of nutritional intervention in elderly subjects after hip fracture: a randomized controlled trial. *Osteoporos Int*. 2013;24(1):151–162.
61. Barton GR, Sach TH, Jenkinson C, Doherty M, Avery AJ, Muir KR. Lifestyle interventions for knee pain in overweight and obese adults aged ≥45: economic evaluation of randomised controlled trial. *BMJ*. 2009;339(7721):610–612.
62. Broekhuizen K, Van Wier MF, Koppes LLJ, et al. An economic evaluation alongside a randomized controlled trial evaluating an individually tailored lifestyle intervention compared with usual care in people with familial hypercholesterolemia. *BMC Res Notes*. 2015;8(1):1–9.
63. Eriksson J, Lindström J, Valle T, et al. Prevention of type II diabetes in subjects with impaired glucose tolerance: the Diabetes Prevention Study (DPS) in Finland: study design and 1-year interim report on the feasibility of the lifestyle intervention programme. *Diabetologia*. 1999;42(7):793–801.
64. Goldfield GS, Epstein LH, Kilanowski CK, Paluch RA, Kogut-Bossler B. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. *Int J Obes*. 2001;25(12):1843–1849.
65. Herman PM, Szczurko O, Cooley K, Seely D. A naturopathic approach to the prevention of cardiovascular disease: cost-effectiveness analysis of a pragmatic multi-worksite randomized clinical trial. *J Occup Environ Med*. 2014;56(2):171–176.
66. Kaplan RM, Hartwell SL, Wilson DK, Wallace JP. Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. *J Gen Intern Med*. 1987;2(4):220–228.
67. Leigh JP, Richardson N, Beck R, et al. Randomized controlled study of a retiree health promotion program: the Bank of America Study. *Arch Intern Med*. 1992;152(6):1201–1206.
68. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779–785.
69. Redman LM, Gilmore LA, Breaux J, et al. Effectiveness of SmartMoms, a novel eHealth intervention for management of gestational weight gain: randomized controlled pilot trial. *JMIR mHealth uHealth*. 2017;5(9):e133.
70. Sikand G, Kashyap ML, Wong ND, Hsu JC. Dietitian intervention improves lipid values and saves medication costs in men with combined hyperlipidemia and a history of niacin noncompliance. *J Am Diet Assoc*. 2000;100(2):218–224.
71. Smith KJ, Kuo S, Zgibor JC, et al. Cost effectiveness of an internet-delivered lifestyle intervention in primary care patients with high cardiovascular risk. *Prev Med (Baltim)*. 2016;87:103–109.
72. Sukhanova A, Ritzwoller DP, Alexander G, et al. Cost analyses of a web-based behavioral intervention to enhance fruit and vegetable consumption. *Int J Behav Nutr Phys Act*. 2009;6:1–8.
73. Toobert DJ, Glasgow RE, Strycker LA, Manuel B, Ritzwoller DP, Weidner G. Long-term effects of the Mediterranean lifestyle program: a randomized clinical trial for postmenopausal women with type 2 diabetes. *Int J Behav Nutr Phys Act*. 2007;4(1).
74. Troyer JL, McAuley WJ, McCutcheon ME. Cost-effectiveness of medical nutrition therapy and therapeutically designed meals for older adults with cardiovascular disease. *J Am Diet Assoc*. 2010;110(12):1840–1851.
75. Wylie-Rosett J, Swencionis C, Ginsberg M, et al. Computerized weight loss intervention optimizes staff time: the clinical and cost results of a controlled clinical trial conducted in a managed care setting. *J Am Diet Assoc*. 2001;101(10):1155–1162.
76. Befort CA, Donnelly JE, Sullivan DK, Ellerbeck EF, Perri MG. Group versus individual phone-based obesity treatment for rural women. *Eat Behav*. 2010;11(1):11–17.
77. Emmons KM, McBride CM, Puleo E, et al. Project PREVENT: a randomized trial to reduce multiple behavioral risk factors for colon cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(6):1453–1459.
78. Franz MJ, Splett PL, Monk A, et al. Cost effectiveness of medical nutrition in patients with DM type 2. *J Am Diet Assoc*. 1995:1018–1024.
79. Glasgow RE, La Chance PA, Toobert DJ, Brown J, Hampson SE, Riddle MC. Long term effects and costs of brief behavioural dietary intervention for patients with diabetes delivered from the medical office. *Patient Educ Couns*. 1997;32(3):175–184.
80. Dalziel K, Segal L. Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. *Health Promot Int*. 2007;22(4):271–283.
81. Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care*. 2001;24(4):619–624.
82. Pritchard DA, Hyndman J, Taba F. Nutritional counselling in general practice: a cost effective analysis. *J Epidemiol Community Health*. 1999;53(5):311–316.
83. Bray GA, Polonsky KS, Watson PG, et al. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22(4):623–634.
84. The Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care*. 2002;25(12):2165–2171.
85. Tuomilehto J, Lindstrom J, Eriksson J, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. 2001;344(18):1343-1350.
86. Chatterton M Lou, Mihalopoulos C, O'Neil A, et al. Economic evaluation of a dietary intervention for adults with major depression (the "SMILES" trial). *BMC Public Health*. 2018;18(1):1–11.

87. Milte R, Miller MD, Crotty M, et al. Cost-effectiveness of individualized nutrition and exercise therapy for rehabilitation following hip fracture. *J Rehabil Med*. 2016;48(4):378–385.
88. Sharma Y, Thompson C, Miller M, et al. Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial. *BMC Geriatr*. 2018;18(1):1–13.
89. Wylie-Rosett J, Herman WH, Goldberg RB. Lifestyle intervention to prevent diabetes: intensive and cost effective. *Curr Opin Lipidol*. 2006;17(1):37–44.
90. Bilvick Tai BW, Bae YH, Le QA. A systematic review of health economic evaluation studies using the patient's perspective. *Value Health*. 2016;19(6):903–908.
91. Glechner A, Keuchel L, Affengruber L, et al. Effects of lifestyle changes on adults with prediabetes: a systematic review and meta-analysis. *Prim Care Diabetes*. 2018;12(5):393–408.
92. Lenoir-Wijnkoop I, Dapoigny M, Dubois D, et al. Nutrition economics: characterising the economic and health impact of nutrition. *Br J Nutr*. 2011;105(1):157–166.
93. Freijer K, Lenoir-Wijnkoop I, Nuijten MJ, Evers SM, Molsen EL. Nutrition economics: an introduction. *Ispor Connect*. 2014;20(4):10–11.
94. van Rijckevorsel-Scheele J, Willems RCWJ, Roelofs PDDM, Koppelaar E, Gobbens RJJ, Goumans MJBM. Effects of health care interventions on quality of life among frail elderly: a systematized review. *Clin Interv Aging*. 2019;14:643–658.
95. Bush CL, Blumberg JB, El-Sohemy A, et al. Toward the definition of personalized nutrition: a proposal by the American Nutrition Association. *J Am Coll Nutr*. 2020;39(1):5–15.
96. Celis-Morales C, Livingstone KM, Marsaux CFM, et al. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. *Genes Nutr*. 2015;10(1).
97. Bandurska E, Damps-Konstańska I, Popowski P, et al. Cost-effectiveness analysis of integrated care in management of advanced chronic obstructive pulmonary disease (COPD). *Med Sci Monit*. 2019;25:2879–2885.
98. Bell CM, Urbach DR, Ray JG, et al. Bias in published cost effectiveness studies: systematic review. *Br Med J*. 2006;332(7543):699–701.
99. Corso P, Hammitt J, Graham J, Dicker R, Goldie S. Assessing preferences for prevention versus treatment using willingness to pay. *Med Decis Making*. 2002;22(5 Suppl):S92–S101.
100. Fischer ARH, Berezowska A, Van Der Lans IA, et al. Willingness to pay for personalised nutrition across Europe. *Eur J Public Health*. 2016;26(4):640–644.
101. Drummond M, Fattore G. Do nutrition interventions require a different approach to economic evaluation? *Value Health*. 2016;19(7):A836–A837.
102. Marsh K, Ijzerman M, Thokala P, et al. Multiple criteria decision analysis for health care decision making: emerging good practices: report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19(2):125–137.
103. Thokala P, Devlin N, Marsh K, et al. Multiple criteria decision analysis for health care decision making: an introduction: report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19(1):1–13.