Master Thesis

Positive Health: A Systematic Review of Cost-effectiveness and Case Studies in the Netherlands

UNIVERSITY OF TWENTE.

Rijnstate

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Master Health Sciences

Track: Optimization of Healthcare Processes

August 2018

Master Thesis Health Sciences

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Rijnstate Hospital

Date: 29-08-2018

Course code: 2017-201600036

Contents

Acknowledgements

The contents of this report are the result of my master thesis assignment for the study programme Health Sciences at the University of Twente. The assignment was carried out on behalf of Rijnstate Hospital in Arnhem, the Netherlands, of which, at the time of writing, my first supervisor, W.H. van Harten, is the director. My thesis is written in the form of an article, with the intention of submitting it to The Lancet Public Health. Before that, though, first some words of thanks, followed by a short description of the process that I went through over the past half year will be provided.

I would like to express my sincere gratitude to both my supervisors for their guidance and constructive criticism during the time that I worked on my master thesis. Through our meetings I believe I have been able to significantly improve my skills in reporting data and finding ways to present them in a clear overview. In addition to that, I have learned numerous things about the way reimbursement decisions come about in practice. Furthermore, I would like to thank M. Rinkes and K. Ruiter-Smit for helping me get started on my assignment, providing interesting learning opportunities, and helping me get in contact with project managers of other pioneer sites. Additionally, I would like to thank all those whom I interviewed for their time and cooperation.

I would also like to offer my sincere gratitude to my parents and friends, for their support and encouragement, and for the conversations that helped me get past some points where I got stuck and was having some difficulty figuring out how to move on.

- Guido Peters

Deventer, July

The process

For the first meeting with my first supervisor, my main goal was to confirm whether or not my interpretation of the assignment was correct. To that end, before the first meeting, I did some preliminary research into the various components that would in my mind make up the end product: product and service development processes, early stage cost-effectiveness assessment, and alternative means of finance.

During the first meeting, it seemed I was thinking in the right direction, and my first supervisor introduced me to a number of people at the hospital who were involved in the prevention project at Rijnstate hospital (GO!), so that I could get some background on the assignment. I made appointments with all of them as soon as possible, and through my conversations with them, I felt that what I had in mind could indeed be helpful for them. Thus, I carried on with my plan to put together a theoretical framework for developing sustainable and cost-effective hospital-based prevention activities, and to conduct a case study on the project aimed at the prevention of childhood obesity at Rijnstate hospital, as well as to perform a systematic literature review on the cost-effectiveness of combined lifestyle interventions. During this time, I was also asked to assess the completeness of a societal cost-benefit analysis of GO!, and to give my opinion on it, as well as on the business case that had been made for it.

Once the theoretical framework was mostly done, the focus shifted to performing a systematic literature review on the cost-effectiveness of combined lifestyle interventions, and collecting information on existing business models for providing hospital-based prevention activities. Before starting on the systematic review, at the recommendation of my supervisors, I discussed my search strategy and the results of a sample search with the information specialist of the Faculty of Science and Technology. It turned out that, while the strategy was sound for the most part, the syntax that I had used was not, and I learned a great deal about the way that the databases for scientific articles work. From this I also learned that it should not be necessary to search multiple databases, as the articles are supposedly present in each database, with the only differences being the way in which searches can be executed and search results are presented.

Subsequently, I performed the search using only Scopus, which still put out 3552 search results. Although scanning the titles and abstracts took very long in the beginning, I learned to approach it more strategically after some time, which significantly sped up the process, and would likely be helpful in the future if I ever need to perform a systematic review again. The same was true for checking full text articles for eligibility. For data extraction, I first made a data template in Microsoft Excel for data that I knew were necessary, and some which I thought might be useful, based on the first few articles that I read. Despite this, however, it happened multiple times that I encountered another characteristic that I wanted to include in the data, causing me to have to go back and forth numerous times. Also, due to

the amount of information provided in economic evaluations, I had to choose between using multiple rows for the same article and putting all the information in the same row. I tried both and eventually decided to put all the data in a single row. This ended up becoming quite cluttered and confusing, however, so in hindsight it might have been better to use different rows.

The intention was originally to also perform a Budget Impact Analysis (BIA). Optimally, one would have access to the Decision Analytic Model (DAM) used in a preceding Cost-Effectiveness Analysis (CEA) so that the impact of reimbursing any particular intervention on the budgets of different budget holders can be estimated for different time horizons and discount rates. However, as this was not the case here, the idea was to use cost-data for GO! and estimates for health effects, costs, and benefits for different time horizons from the systematic literature review to populate a BIA instead. However, while performing a BIA in such a way would result in great uncertainty anyway, interventions were too heterogeneous to allow for even that. Because of that, the idea of performing a BIA for GO! was eventually abandoned.

While data extraction for the systematic literature review was nearing completion, interviews with project managers at the pioneer sites and a nearby hospital were planned, and conducted over the course of approximately two weeks. Following that, I transcribed all the interviews, which took me significantly longer than I had planned for. Once that was done, I started writing the results section. After having submitted my first draft, my first supervisor decided that the results were interesting enough to attempt to get them published. Therefore, my thesis comes in the form of an article, and the framework for developing sustainable and cost-effective prevention activities was left for what it was, and is only included in Appendix D. While trying to improve the results section, I was experiencing some difficulty giving meaning to the results. Meetings with my supervisors reminded me that I would need to make choices regarding which results to present and which not to present, and provided me with guidance on how one could provide more information without a need for more space.

Finally, it took some time to get the discussion right. At first, it lacked structure and mainly summarised the results section. After structuring it more clearly, and in such a way that it was in line with the introduction, it was still dominated by summaries rather than points of discussion. In the final version, the summarising portions have been minimised, and all points that appeared of interest to me have been raised.

Following this short explanation of the process that I went through to write my thesis, the article in which the fruits of my research are reported can be found. It is titled: "*Positive Health: A Systematic Literature Review of Cost-Effectiveness and Case Studies in the Netherlands*".

Positive Health: A Systematic Review of Cost-effectiveness and Case Studies in the Netherlands

Guido Maarten Peters

Summary

Background Rising healthcare costs are an increasing concern in developed countries, due to increased life expectancy, aging populations, and the increasing prevalence of chronic diseases and diseases of old age. One way of remedying this that has been suggested by the OECD, among others, is disease prevention. It is questionable, however, whether all disease prevention efforts would be cost-saving. In fact, modelling studies have pointed out that in many cases the opposite is true. If disease prevention does indeed increase cost, it should at least provide good value for money. Also, it is necessary for efficient interventions to be provided sustainably. This is not currently possible in the Netherlands, however, as financing is not available. Therefore, in this article a systematic review of the cost-effectiveness literature of combined lifestyle interventions will be performed, and case studies will be conducted to find out whether sustainable ways of financing hospital involvement in disease prevention exist.

Methods Search terms and inclusion criteria were based on a systematic review of combined lifestyle interventions, adjusted for finding evidence of cost-effectiveness rather than effectiveness, and to find a broader range of interventions. Findings were classified as dominant (better health outcomes at a lower cost), very cost-effective (ICER ≤ $25,000), cost-effective (ICER $25,001 - $50,000), marginally cost-effective (ICER $50,001 - $100,000), and not cost-effective (ICER > $100,000), as done in another systematic review of economic evaluations.
Case studies consisted of conducting semi-structured interviews with project managers and other representatives of pioneer sites and one local non-pioneer site hospital, as well as reviewing the websites of interventions and documents pertaining to the development or implementation of interventions and the national approach to dealing with childhood obesity.

Results The search delivered 31 articles that met inclusion criteria. Dominant, very cost-effective, cost-effective, and not cost-effective interventions were reported in six, 20, two, and three articles, respectively. Due to the heterogeneity of results, they are only discussed qualitatively. They are presented according to the study focus, diabetes prevention, obesity prevention, or other, and by whether the intervention was conducted in an individual or group modality. Studies focusing on diabetes prevention generally reported greater effects at a greater cost than studies focusing on obesity prevention. The same was true for individual interventions as compared to group interventions.
Furthermore, seven case studies were conducted, of which five at pioneer sites. In three cases formal evaluations had been conducted by hospitals, which seemed to agree with the literature. Financing of development came mainly from hospitals' own budgets and subsidies awarded for the particular project that was being developed. No means of financing that seemed to be truly sustainable were found.

Interpretation It seems that combined lifestyle interventions are good value for money, and have the potential to be cost-saving. To further develop cost-effective disease prevention activities, however, sustainable financing for hospital involvement needs to become available, as hospitals may have an important role in formally evaluating interventions. More research is necessary to find ways in which this could be achieved.

1. Introduction

As life expectancy is increasing, populations are aging, and chronic diseases and diseases of old age are becoming more prevalent, rising healthcare costs are an increasing concern of governments in developed countries. For example, healthcare expenditure in the US went from 6.2% of GDP in 1970 to 17.2% in 2016, and in the Netherlands it went from 5.7% of GDP in 1972 to 10.5% in 2016.[1] Multiple approaches to remedy this issue have been proposed, one of which is disease prevention.[2]

It has been debated whether or not preventing disease would really reduce healthcare costs, as prevention of disease will likely result in extended life expectancy, which in turn generally results in medical expenses that would not have occurred otherwise.[3] However, a recent study found that prevention can reduce healthcare costs, while at the same time extending life expectancy, if the disease that is targeted by the prevention effort does not have too great of an effect on mortality.[4] Diseases that were found to meet these criteria include diseases of the circulatory system, coronary heart disease, and diseases of the digestive system.[4]

Hospitals in the Netherlands have expressed interest in disease prevention. However, efforts towards disease prevention based out of hospitals are not reimbursed in the current situation. To ensure continuity of hospital based efforts in the domain of disease prevention, it is thus necessary to find a sustainable financing model.

To explore whether or not there is potential for a positive business case in disease prevention, the cost-effectiveness of combined lifestyle interventions was reviewed, and ways in which such interventions are currently provided in the Netherlands were studied.

2. Methods

As Cost-Effectiveness Analyses (CEAs) and Budget Impact Analyses (BIAs) are increasingly demanded by reimbursement authorities as part of listing submissions,[5] a systematic review of the cost-effectiveness literature on combined lifestyle interventions was performed. The review was meant to find as broad of an evidence base as possible regarding cost-effectiveness. This allows assessing whether combined lifestyle interventions have potential for a positive business case when applied to a variety of conditions.. In this systematic review, cost data will be presented as absolute costs rather than incremental costs (unless otherwise mentioned), to enable a potential future BIA. While a BIA was not conducted as part of this article, some comments regarding budget impact are made.

Furthermore, a case study on an approach to treating and preventing obesity that is being developed in the Netherlands was conducted. This approach consists of influencing nutritional and physical activity behaviours, akin to a combined lifestyle intervention. The goal of this case study was to find out what the role of hospitals in prevention activities is at present, and what ways are being used to finance such activities. The case study was conducted by interviewing project managers at pioneer sites where implementation of the approach is being tested, supplemented by desk research.

2.1. Systematic literature review

The published literature on the cost-effectiveness of combined lifestyle interventions was searched using Scopus (date of last search: 04-30-2018). Search terms used were a combination of "obesity treatment", "obesity prevention", "obes*" "behavioural weight management programme", "BWMP", "cost*", "cost-effectiveness", "cost-utility", and "cost-benefit". Inclusion criteria were determined according to the PICO method (see below), and were based to some extent on a systematic review on the effectiveness of long-term weight management schemes for adults conducted in 2013.[6] The selection was verified through independent assessment of a 20% sample by the second author, producing complete agreement.

Population: Studies will only be included if they do not focus on individuals with a pre-existing condition.
Intervention: Interventions must include diet, physical exercise, and behavioural change strategies, must contain personal contact, and studies must have a follow-up of at least 12 months to be included. Studies evaluating pharmaceutical or surgical treatment will be excluded, as the focus of this systematic review is on combined lifestyle interventions.
Comparator: The comparator must be standard practice, no intervention, leaflet(s) only, or a one-off session.
Outcome: The outcome must be a full economic evaluation, i.e. a cost-effectiveness analysis, cost-utility analysis, or cost-benefit analysis, meaning that costs must be expressed in monetary terms and effects in QALYs or DALYs.[7]
Cost data are reported as absolute costs rather than incremental costs, and were converted to 2016 US dollars using the cost converter developed by the CCEMG and the EPPI-centre,[8] as recommended by Van Mastrigt et al.[7]
Finally, only English and Dutch articles were included.

2.2. Case studies

Project managers of all eight pioneer sites were sent a request for an interview, accompanied by a description of the goal of the research. A hospital in the vicinity of one of the pioneer sites was also contacted, as it was known to the authors' network that they, too, had a number of projects regarding childhood obesity. The interviews were conducted following a semi-structured format, and the participants were sent a document containing a short introduction to the research as well as the general line of questioning (Table 1) a day in advance, save for two cases. Permission to record the interviews was granted in all cases, however two interviews were conducted by phone and could not be recorded at the time as a result. Recordings were transcribed before results were processed. In those cases where recording the interview was not possible, notes were taken to the best of the interviewer's ability. Additionally, desk research was conducted, consisting of the reviewing of websites and available documents pertaining to the development and implementation of the approach.

What are the key components of your programme?
Have these always been this way or have there been changes?
What is the envisioned role of the hospital in the programme?
What resources do you need to realise the programme?
Who do you (want to) collaborate with in delivering the programme?
How do children get into the programme?
Who purchases your programme?
Who pays for your programme? (purchaser / other party / multiple payors?)
What does the hospital get paid for?
What are the main sources of expenditure?

Table 1. Interview questions

3. Results from the systematic review of cost-effectiveness of lifestyle interventions

3.1. Literature search

In the main search of Scopus, 3,552 articles were found. After screening the titles and abstracts of these articles, 70 were selected for full text retrieval. In all other cases, it was evident from the title or abstract that it did not concern a combined lifestyle intervention as per the criteria used in this article, i.e. it was meant to influence only physical activity or dietary behaviours. Using the snowballing technique, particularly in other systematic reviews, resulted in an additional 17 articles selected for full text retrieval, for a total of 87 articles, of which 31 articles met the inclusion criteria.

Articles were excluded for a number of reasons: the intervention did not meet inclusion criteria or was insufficiently described to determine whether or not inclusion criteria were met (n=14), no full economic evaluation was reported (n=9), ICERs were not reported in terms of costs per QALY gained or cost per DALY averted (n=4), the study was a duplicate (n=3), and other reasons (n=11). The study

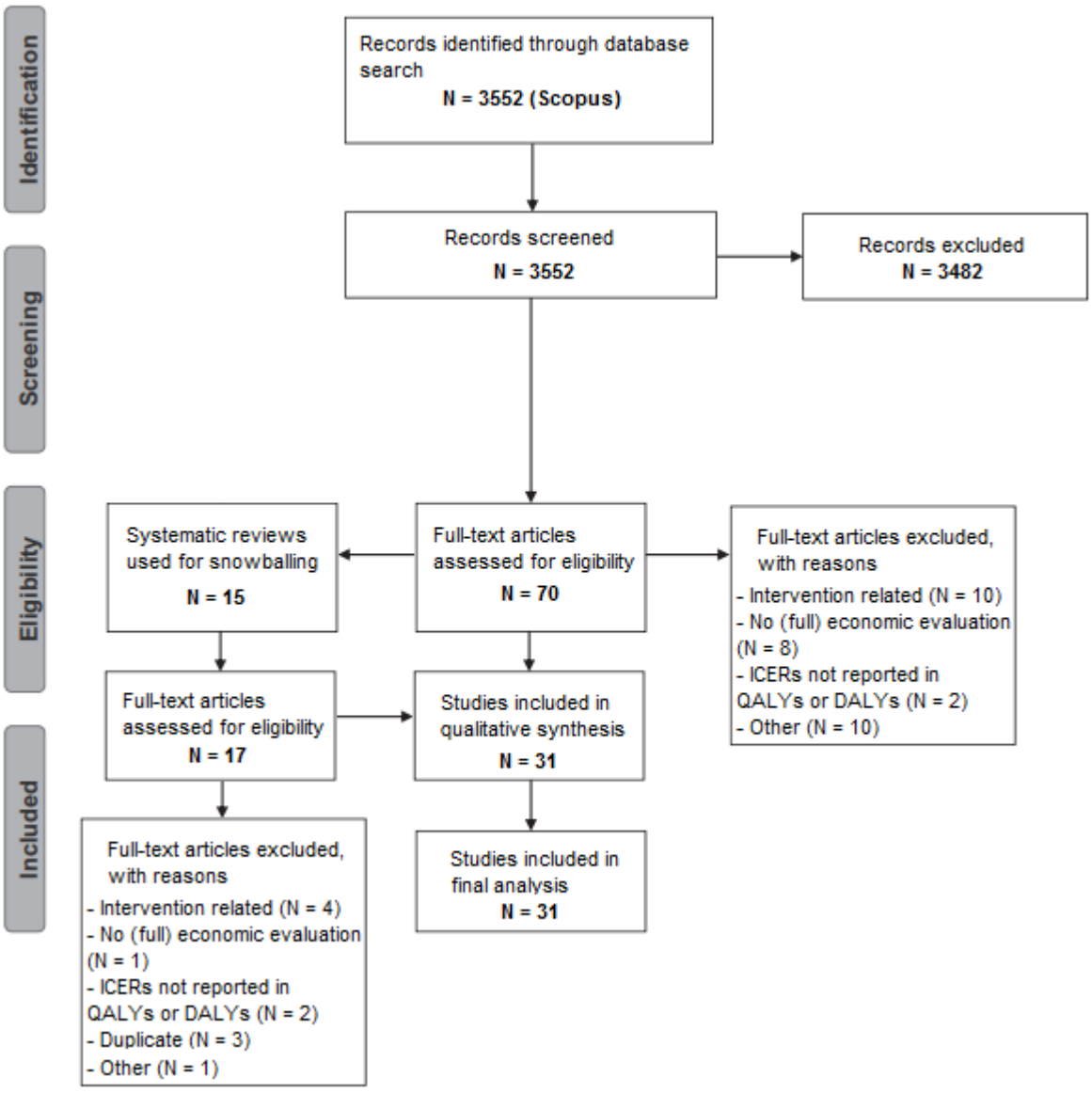


Figure 1. Study selection flowchart

selection process is represented by the flowchart in Figure 1.
A complete list of the excluded articles of those selected for full text retrieval as well as reasons for their exclusion is available in Appendix A.

3.2. Study characteristics

Of the 31 included articles, eight reported cost-effectiveness data based directly on empirical data, while the remaining 23 took a modelling approach to determine cost-effectiveness of interventions. Most of the modelling studies that were found used Markov models, with time horizons varying from 1 year to lifetime. Simulations also differed regarding the age and prevalence of risk factors for diabetes and cardiovascular disease among the simulated populations, as well as the extent of the consequences of obesity that were taken into account in the calculation of ICERs.
Most articles studied interventions in a primary care setting (N=12), followed by hospital settings (N=8), and community settings (N=4). One article studied interventions in both a primary care and a community setting. Other settings studied included general practices (GPs) and schools, which were each studied by one article. In four articles it was not clear what the setting of the intervention was. An overview of this and the role of the hospital in each of the interventions can be found in Appendix B.
The focus of included articles was most often on diabetes prevention (N=16), followed by obesity treatment or prevention (N=11), with other areas of focus being metabolic syndrome prevention (N=1), cardiovascular disease prevention (N=1), problematic behaviour in children(N=1), and reducing the prevalence of overweight on the population level (N=1).
Another factor that varied substantially between studies was the assumptions regarding the duration of intervention effects, ranging from the effect being permanent to the effect only being present for the length of the intervention. Discount rates varied between 1.5% and 5%, with 3% being the most common (N=16). Also, some studies discounted health outcomes and costs according to different rates.
Furthermore, 19 distinct interventions were identified, of which 12 were group-based, four were individual interventions, and in the remaining three it was unclear whether the intervention was delivered in an individual or group setting. Descriptions of the interventions can be found in Appendix A.
Out of the interventions identified, the US Diabetes Prevention Program and Weight Watchers were the most studied, being the subject of nine and five included articles respectively. Additionally, cost-effectiveness was approached from societal, modified societal (mainly not including participant time), health system, and third party payer perspectives. National contexts also differed across studies, with most studies conducted in a US context (N=12), followed by the UK (N=7) and Australia (N=6). Studies were also carried out in the contexts of France, Germany, Switzerland, Sweden, the Netherlands, and Spain. A full overview of study contexts is also included in Appendix B.

3.3. Budget impact and coverage

Only one paper reported on budget impact. It investigated the impact of the DPP when applied to individuals with impaired glucose tolerance at the age of 50 on the budgets of private health insurers and Medicare.[9] If all intervention costs were paid by private insurers, as would normally have been the case in this age group, 15-year incremental costs of $3920 were found for private insurers, while Medicare would experience lifetime cost savings. Costs payable by private insurance to achieve a 3-year ROI and by Medicare to maintain cost neutrality were calculated, which resulted in 56% of intervention costs being covered. The rest would then have to be paid by individual consumers or their employers.

Most articles did report resource use, which could be used to compute the budget impact of the particular intervention studied in any given article for the relevant context, however, this would be limited to the time horizon(s) for which data are reported. Calculating budget impact for other time horizons would require a full simulation model. Also, indirect costs prevented by the intervention were in many cases not included extensively.

3.4. Cost and effectiveness results

In the following sections the results will be discussed separately for the different areas of focus, i.e. diabetes prevention, obesity treatment and prevention, and others. Individual and group interventions will also be considered separately. Furthermore, a categorisation of the level of cost-effectiveness that has been used in another systematic review will be used.[10] Interventions will be categorised as dominant (improved health outcomes at a lower cost), very cost-effective (≤ $25,000 per QALY gained or DALY averted), cost-effective ($25,001 to $50,000 per QALY gained or DALY averted), marginally cost-effective ($50,001 to $100,000 per QALY gained or DALY averted), and not cost-effective (> $100,000 per QALY gained or DALY averted). QALYs gained are reported on a per participant basis, unless otherwise stated. Finally, cost data will be presented as absolute costs rather than incremental costs, unless otherwise indicated.

3.4.1. Diabetes prevention

Of the articles focusing on diabetes prevention (N=16), four reported cost-effectiveness based on empirical outcomes.[11-14] Two of these reported data at ten year follow-up,[13,14] though they both used the same sample, with one focusing on the subsample of individuals that adhered to the intervention.[14] Both reported QALYs gained of 0.15 and ICERs in the very cost-effective category. The other two had follow-up data at three and four years,[11,12] and both reported < 0.1 QALYs gained. Nonetheless, one of the articles reported an ICER in the very cost-effective category,[12] while the other reported the ICER to be in the cost-effective category.[11]

Of the 12 articles included that made use of modelling, two employed a time horizon less than lifetime.[15,16] One applied a 10 year time horizon, reporting QALYs gained of < 0.1, and producing cost savings, putting this intervention in the dominant category.[16] The other applied a 30 year time horizon in the main analysis, resulting in 0.16 QALYs gained, with an ICER in the not cost-effective category.[15]

In the remaining ten articles that used modelling, QALYs gained < 0.1 were reported once, accompanied by cost savings, making this intervention dominant as well.[22] Six articles reported QALYs gained between 0.1 and 0.5,[9,18-20,23,25] four of which reported ICERs in the very cost effective category,[9,18,20,25] with the remaining two reporting interventions to be dominant.[19,23] Two articles reported QALYs gained > 0.5 and both found ICERs to be in the very cost-effective category.[17,21]

Finally, one article reported QALYs gained per million individuals in the general population, while the intervention was only applied to part of the population.[24] This resulted in an extremely low estimate of 0,00022 QALYs gained, with the ICER being in the very cost-effective or dominant category, depending on risk-group targeted.[24]

A full overview of the results from these articles is provided in Table 2.

Table 2. Results from articles focusing on diabetes prevention

Source	Method	QALYs (incremental)	Costs	ICER	Discounting	Time horizon / follow-up	Comparator / intervention (see Appendix A)
DPPRG, 2003[11]	Empirical (N_i =910; N_c=932)	0,072	$3950	$42,640; in groups of 10: $12180	3%	3 years	30-minute annual education session and placebo pills / intervention #1
Sagarra R, 2014[12]	Empirical (N_i =333; N_c =219)	0,012119	$1170	$5060	Not reported	4 years	General written and oral information and an exercise session at base-line and subsequent annual visits / intervention #2
Herman WH, 2013[13]	Empirical (N_i =587; N_c =932)	0,15	$5270 (over 10 years, undiscounted)	$21,890	3%	10 years	30-minute annual education session and placebo pills / intervention #1
DPPRG, 2013[14]	Empirical (N_i =910; N_c =932)	0,15	$5040 (over 10 years, undiscounted)	$11,750 / $14,100 (Undiscounted / discounted) for individual DPP; $580 / $1620 for group DPP	3%	10 years	30-minute annual education session and placebo pills / intervention #1
Eddy DM, 2005[15]	Modelling (Archimedes model)	0,159	$1840 for the first year, $910 / year thereafter (incremental)	$193,580 (health plan, including 10% annual turnover rate)	3%	30 years	30-minute annual education session and placebo pills / intervention #1
Hoerger TJ, 2015[16]	Modelling	0,0422	$530	Cost-saving -$550 (ICER of $21,680 at a cost of $1460)	3%	10 years	Do nothing, rates observed in general population applied / intervention #3
Herman WH, 2005[17]	Modelling	0,57	$860 incremental ($6680 societal)	$1490 ($11,910 societal)	3%	Lifetime	30-minute annual education session and placebo pills / intervention #1
Ackermann RT, 2006[9]	Modelling	0,3 ; 0,29	$9540 (private insurer) ; $2000 (Medicare)	$13,060 ; cost-saving (-$2890)	3%	Lifetime	30-minute annual education session and placebo pills / intervention #1
Hoerger TJ, 2007[18]	Modelling	0,118 ; 0,099 (both IFG AND IGT ; either IFG OR IGT)	$1620 + $812 / year (incremental)	$10,830 ; $12,590 (both IFG AND IGT ; either IFG OR IGT)	3%	Lifetime	No additional treatment, not described further / intervention #1
Lindgren P, 2007[19]	Modelling	0,2	$3340	cost-saving (-$2370)	3%	Lifetime (implied, not specifically stated)	General oral and written information on diet (2-page leaflet) and physical exercise at baseline and subsequent annual visits / intervention #4
Jacobs-van-der-Bruggen MAM, 2007[20]	Modelling	,27 to 1,17	€ 700	€ 3900	4% (costs); 1,5% (effects)	Lifetime	30-minute annual education session and placebo pills / intervention #5
Schaufler TM,	Modelling	2,91	$2400	$820	5% (costs	Lifetime	Annual 30-minute education session / inter-

2010[21]					only)		vention #1
Neumann A, 2011[22]	Modelling	0,02 (men ages 30 and 70, women ages 50 and 70) to 0,03 (men age 50, women age 30) pp	$560 year 1 + €270 / year of follow-up	-$36,370, -$21,830, $39,800 (men 30, 50, 70); -$45,390, -$30,660, $28,080 (women 30, 50, 70)	3%	Lifetime	No intervention, not described further / intervention #6
Palmer AJ, 2012[23]	Modelling	0,39	$2710 + $30/year	Dominant ($2110 when costs increase by 20%; $7450 when using an average progression rate from IGT to T2D)	5%	Lifetime	Treatment of T2DM after diagnosis / intervention #1
Breeze PR, 2017[24]	Modelling	0,00022 to 0,00073 / million of general population	-$1,2; -$0,3; -$0,3 (if cost is spread over 1 million people)	$480 (or dominant over alternatives)	1,50%	Lifetime	No interventions, rates observed in general population applied / intervention #7
Roberts S, 2018[25]	Modelling	0,23	$940 ; $1480 ; $1550	$4030 (IGT), $9900 (IFG), $10,700 (HbA1c)	3,50%	Lifetime	Usual care, not described further / intervention #8

Health system perspective; Societal perspective

3.4.2. Obesity prevention and treatment

Of the articles focusing on prevention and treatment of obesity (N=11), four reported cost-effectiveness analysis based on outcomes at one year.[26-28,31] Three of these were empirical studies,[26-28] and one was a modelling study.[31] One of the empirical studies did not separately report the number of QALYs gained, but did report ICERs per QALY gained in the very cost-effective category, except when implementation of the intervention was modelled for Germany, which ended up in the cost-effective class.[26] The other two empirical studies both reported QALYs gained to be < 0.1,[27,28] with one reporting the ICER to be in the very cost-effective category,[27] while the other was reported in the not cost-effective category.[28] The modelling study also reported < 0.1 QALYs gained at a one year time horizon, with an ICER in the very cost effective category.[31]

One modelling study reported neither a discount rate, nor a time horizon explicitly, though a one year time horizon was implied. This study found < 0.1 QALYs gained with an ICER in the cost-effective category.[29]

Another modelling study employed a time horizon of 25 years, and also found QALYs gained < 0.1, though again with an ICER in the very cost-effective category.[30]

The remaining six modelling studies used a lifetime time horizon.[31-36] Among these articles, QALYs gained < 0.1 were reported once, though the intervention did produce cost savings and was therefore in the dominant category.[36] Three of these articles reported QALYs gained between 0.1 and 0.5,[31-33] with ICERs reported in the dominant[31] and very cost-effective[32,33] categories. The last two articles reported health outcomes in number of DALYs averted.[34,35] One of them reported < 0.1 DALYs averted with an ICER in the very cost-effective category,[34] while the other reported DALYs averted for the whole population, when the intervention was modelled to be applied to all eligible individuals in the population, resulting in an ICER in the not cost-effective category.[35]

A full overview of the results from these articles is presented in Table 3.

3.4.3. Other areas of focus

One included article focused on prevention of metabolic syndrome.[37] The intervention in this study resulted in 0,01 QALYs gained at an ICER of $3420, placing it in the very cost-effective category.

Another article focused on prevention of cardiovascular disease, and found that the intervention resulted in 0,07 , 0,08 , and 0,20 QALYs gained, using the SF-6D, EQ-5D, and EQ-VAS Quality of Life questionnaires, being dominant over alternatives at the same time.[38] When savings were not counted, ICERs of $5340, $4980, and $1850 respectively were achieved.

Yet another article focused on reducing the prevalence of overweight and obesity on the population level, and found lifestyle intervention implemented on such a level to be very cost-effective, at an ICER of $10,590.[39] Costs of the intervention and QALYs gained were not reported at the individual level, however, making it difficult to compare to other results discussed in this article.

Finally, one article was included that focused on behavioural problems associated with obesity, in that it aimed also to reduce interaction with the judiciary system and unemployment, as well as to improve graduation rates in high-poverty urban schools.[40] This intervention was reported to produce an additional 0,27 QALYs, while being cost-saving.[40]

A full overview of the results from these articles is provided in Table 4.

Table 3. Results from articles focusing on obesity prevention and treatment

Source	Method	QALYs gained / DALYs averted	Costs	ICER	Dis-counting	Time hori-zon / Fol-low-up	Comparator / intervention (see Appendix A)
Fuller NR, 2013[26]	Empirical (N_i=230; N_c=214)	Not reported	$540 / $410 / $670	$12840 / $11340 / $39750	n.a.	1 year	One 20-minute consultation with a nurse, costed for GP / intervention #9
McRobbie H, 2016[27]	Empirical (N_i =197; N_c =94)	0,0104	$290	$11710	n.a.	1 year	Four one-hour sessions delivered by a nurse over the course of 8 weeks / intervention #11
Robertson W, 2017[28]	Empirical (N_i =56; N_c =59)	0,0009	$770	$818830	n.a.	1 year	Weekly 90-minute sessions consisting of a healthy eating and physical activity workshop for 10-12 weeks / intervention #12
Finkelstein EA, 2014[29]	Modelling	0,011 (0,008 to 0,013)	$380	$34630	Not re-ported, n.a. im-plied	Not explicitly reported, 1 year is im-plied	Low-intensity intervention, not further described as it used meta-analyses / intervention #9
Ahern AL, 2017[30]	Modelling	0,01282 pp	$280	$3490	3,50%	25 years	Given a booklet containing self-help information regarding weight management / intervention #9
Meads DM, 2014[31]	Modelling	0,06 ; 0,22	£110; £9060	6900GBP ; cost-saving (920 GBP)	3,50%	1 year; life-time	Oral or written information on diet, physical activity, and lifestyle change / intervention #12
Roux L, 2006[32]	Modelling	0,243	$3820	$12600	3%	Lifetime	Not specified as it uses a meta-analysis of various intervention for input / intervention #13
Galani C, 2007[33]	Modelling	0,33	$990	$20 (Cost-saving in women ages 35 ($1280), 45 ($610), and 55 ($140), and men ages 25 ($11650), 35($41430), 45($7510), and 55($8150) at BMI=30, women age 45 ($1900), and men age 55 ($1370) with BMI=33.)	3%	Lifetime	3 dietitian visits in the first year, 1 annual visit thereafter, two exercise sessions per month in the first year, and one exercise session per month in the subsequent year / intervention #13
Moodie M, 2008[34]	Modelling	0,053 DALYs		$4910	3%	Lifetime	Not specified / intervention #14
Cobiac L, 2010[35]	Modelling	38 DALYs (whole population); 54 DALYs(whole population)	$250; $210	$128500; $138390	3%	Lifetime	Background trend / intervention #15 and #16
Fuller NR, 2014[36]	Modelling	0,03 pp	$210	savings of $50 ($8350 / QALY in a 5 year per-spective)	3,50%	Lifetime	Weight loss advice from a primary care profes-sional at the local GP practice according to Austra-lian, German, and UK guidelines (2013) / interven-tion #9

Health system perspective; Societal perspective; Modified societal perspective

Table 4. Results from articles with other areas of focus

Source	Method	QALYs gained	Costs	ICER	Discount-ing	Time horizon / Follow-up	Comparator / intervention (see Appendix A)
Smith KJ, 2010[37]	Modelling	0,01	$3420 ($50 incremental)	$4630	3%	3 years	30-minute annual education session and placebo pills / intervention #17
Eriksson MK, 2010[38]	Empirical (Ni=58; Nc=62)	0,08 (EQ5D), 0,20 (EQVAS), 0,07 (SF6D)	$460 (of which $230 is paid by the participant)	$4980 ; $1850 ; $5340 (EQ5D ; EQVAS; SF6D)	3%	3 years	Oral and written information at one group meeting / intervention #18
Bemelmans W, 2008[39]	Modelling	Not reported	Not reported	€ 10.590	4%	80 years	Not reported / intervention #5
Hajizadeh N, 2017[40]	Modelling	0,27 pp	$920	Cost-saving ($4430 pp)	5%	Lifetime	NYC DOE pre-k and kindergarten program-ming / intervention #19

Health system perspective; Societal perspective; Modified societal perspective

3.4.4. Individual interventions

In 14 of the included articles, cost-effectiveness outcomes of individual interventions were reported, although it must be noted that the maintenance component of interventions was often group-based. The majority (N=10) of articles on individual interventions were studies on the US Diabetes Prevention Program (USDPP), and a total of four distinct interventions were found.

Three articles reported cost-effectiveness based on empirical outcomes. Of these, one article based its cost-effectiveness analysis on three-year follow-up data, reporting < 0.1 QALYs gained, and an ICER in the cost-effective category.[11] The other two articles based their cost-effectiveness analyses on 10-year follow-up data, both reporting 0.15 QALYs gained and ICERs in the very cost-effective category.[13,14] However, one article performed its analysis using only the adherent portion of the sample that was used in the other article.[13]

The remaining 11 articles reported cost-effectiveness using modelling approaches. One article applied a ten year time horizon, finding < 0.1 QALYs gained, though the ICER was reported in the dominant category.[16] Another article applied a 30-year time horizon, finding QALYs gained of 0.16 and an ICER in the not cost-effective category.[15] Furthermore, one article applied a time horizon of 80 years, but did not report costs or QALYs separately.[39] It did, however, report the ICER per QALY to be in the very cost-effective range.

The other eight modelling studies all used a lifetime time horizon. Six of these found QALYs gained between 0.1 and 0.5, four of which reported ICERs in the very cost-effective category,[9,18,20,33] while two reported ICERs in the dominant category.[19,23] Two modelling studies found QALYs gained of 0.57 and 2.91,[17,21] and both reported ICERs in the very cost-effective category.

An overview of the results from these articles is provided in Table 5.

3.4.5. Group interventions

Of the included articles, 16 discussed group interventions. Of these, five articles reported cost-effectiveness based on empirical outcomes. Three of those used 1-year follow-up data, of which one did not report QALYs gained,[26] and the others found < 0.1 QALYs gained,[27,28] with ICERs in the very cost-effective[26,27] and in the not cost-effective category.[28] The other articles used 3- and 4-year follow-up data, both reporting QALYs gained < 0.1 and ICERs in the very cost-effective category.[38,12] The remaining 11 articles used modelling approaches to calculate cost-effectiveness. One of these did not explicitly report a time horizon, though a one year time horizon was implied.[29] This article reported QALYs gained < 0.1 and an ICER in the cost-effective category. One modelling study investigated cost-effectiveness at one year, finding QALYs gained < 0.1 and an ICER in the very cost-effective category.[31] Another modelling study applied a three year time horizon, finding QALYs gained < 0.1 and an ICER in the very cost-effective category.[37] Furthermore, one article applied a time horizon of 25 years, also reporting QALYs gained < 0.1 and an ICER in the very cost-effective range.[30] The remaining seven modelling studies all applied a lifetime time horizon. Three of these found QALYs gained < 0.1, two of which also reported ICERs in the dominant category,[22,36] with the last one reporting an ICER in the very cost-effective category.[24] Two modelling studies using a lifetime time horizon found QALYs gained between 0.1 and 0.5, and reported ICERs in the very cost-effective and dominant categories.[25,40] Finally, one study reported health outcomes in terms of DALYs averted in the whole population, when implementation of the intervention on a national level was modelled. It reported 38 and 54 DALYs averted for two different interventions, with ICERs in the not cost-effective category. An overview of the results from these articles is provided in Table 6.

Table 5. Results from articles focusing on individual interventions

Source	Method	QALYs gained	Costs	ICER	Dis-counting	Time hori-zon / fol-low-up	Comparator / intervention (see Appendix A)
DPPRG 2003[11]	Empirical (Ni=910; Nc=932)	0,072	$3950	$42640 ($69850) ; in groups of 10 $12180 ($39390)	3%	3 years	30-minute annual education session and placebo pills / intervention #1
Herman WH, 2013[13]	Empirical (Ni=587; Nc=932)	0,15	$5270 (over 10 years, undiscounted)	$ 21.890,00	3%	10 years	30-minute annual education session and placebo pills / intervention #1
DPPRG, 2013[14]	Empirical (Ni=910; Nc=932)	0,15	$5040 (over 10 years, undiscounted)	$11750 / $14100 (Undiscounted / discounted)	3%	10 years	30-minute annual education session and placebo pills / intervention #1
Eddy DM, 2005[15]	Modelling (Ar-chimedes model)	0,159	$1840 for the first year, $910 / year thereafter	$193580 (health plan, including 10% annual turnover rate); $84740 (societal)	3%	30 years	30-minute annual education session and placebo pills / intervention #1
Hoerger TJ, 2015[16]	Modelling	0,0422	$530	Cost-saving (ICER of $21680 at a cost of $1460)	3%	10 years	Do nothing, rates observed in general population applied / intervention #3
Herman WH, 2005[17]	Modelling	0,57	$860 incremental ($6680 societal)	$1490 ($11910 societal)	3%	Lifetime	30-minute annual education session and placebo pills / intervention #1
Ackermann RT, 2006[9]	Modelling	0,3 ; 0,29	$9540 ; $2000	$13060 ; cost-saving	3%	Lifetime	30-minute annual education session and placebo pills / intervention #1
Hoerger TJ, 2007[18]	Modelling	0,118 ; 0,099 (both IFG AND IGT ; either IFG OR IGT)	$1620 + $812 / year (in-cremental)	$10830 ; $12590 (both IFG AND IGT ; either IFG OR IGT)	3%	Lifetime	No additional treatment, not further specified / intervention #1
Lindgren P, 2007[19]	Modelling	0,2	$3340	cost-saving / $3020	3%	Lifetime (implied, not specifically stated)	General oral and written information on diet (2-page leaflet) and physical exer-cise at baseline and subsequent annual visits / intervention #4
Jacobs-van-der-Bruggen MAM, 2007[20]	Modelling	,27 to 1,17	€ 700	€ 3.900	4% (costs); 1,5% (ef-fects)	Lifetime	30-minute annual education session and placebo pills / intervention #5
Schaufler TM, 2010[21]	Modelling	2,91	$2400	$820	5% (costs only, QA-LYs dis-counted in SA)	Lifetime	Annual 30-minute education session / intervention #1

Palmer AJ, 2012[23]	Modelling	0,39	$2710 + $30/year	Dominant ($2110 when costs increase by 20%; $7450 when using an average progression rate from IGT to T2D)	5%	Lifetime	Treatment of T2DM after diagnosis / intervention #1
Galani C, 2007[33]	Modelling	0,33	$990	$20 (Cost-saving in women ages 35 ($1280), 45 ($610), and 55 ($140), and men ages 25 ($11650), 35($41430), 45($7510), and 55($8150) at BMI=30, women age 45 ($1900), and men age 55 ($1370) with BMI=33.)	3% (costs and QALYs)	Lifetime	3 dietitian visits in the first year, 1 annual visit thereafter, two exercise sessions per month in the first year, and one exercise session per month in the subsequent year / intervention #13
Bemelmans W, 2008[39]	Modelling	Not reported	Not reported	€ 10.590	4%	80 years	Not reported / intervention #5

☐ **Health system perspective;** ☐ **Modified societal perspective**

Table 6. Results from articles focusing on group interventions

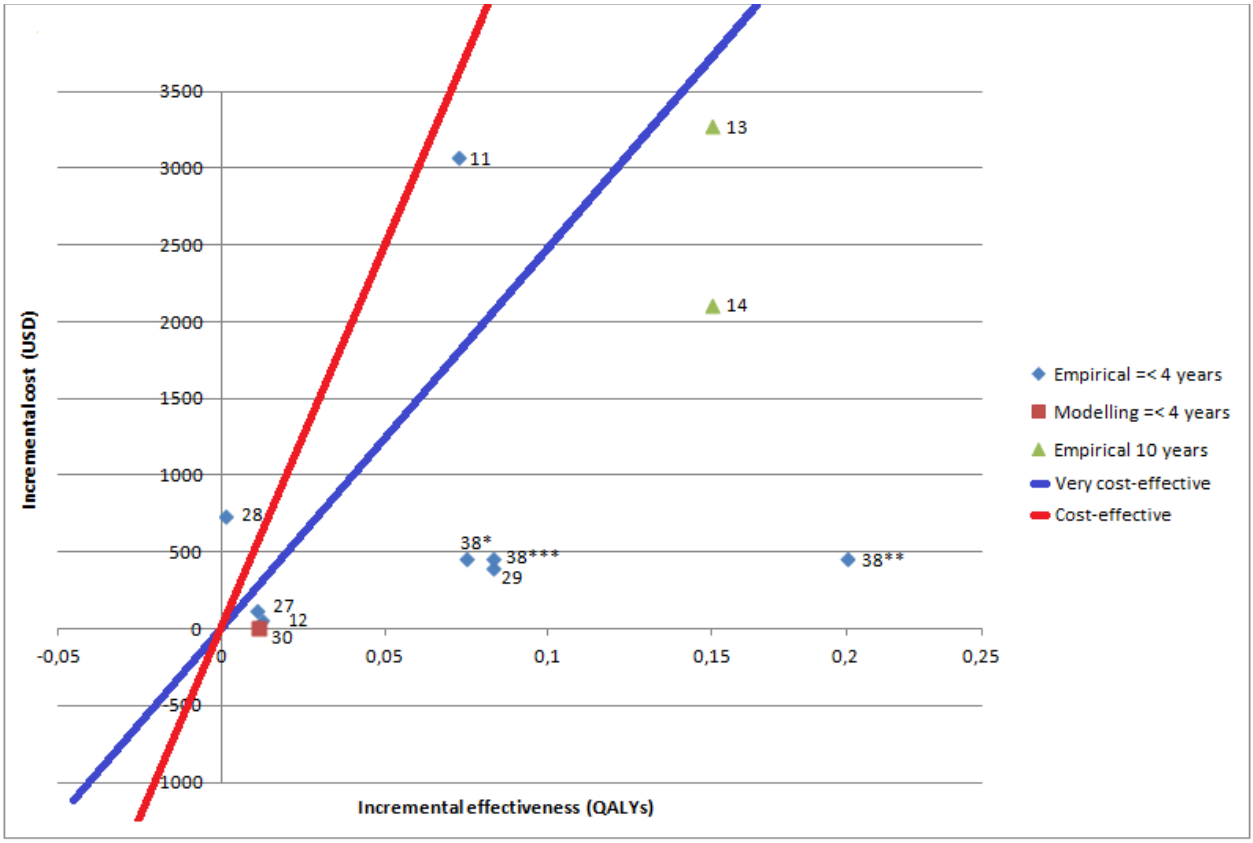
Source	Method	QALYs gained	Costs	ICER	Dis-counting	Time horizon / follow-up	Comparator / intervention (see Appendix A)
Fuller NR, 2013[26]	Empirical (Ni=230; Nc=214)	Not reported	$540 / $410 / $670	$12840 / $11340 / $39750	n.a.	1 year	One 20-minute consultation with a nurse, costed for GP / intervention #9
McRobbie H, 2016[27]	Empirical (Ni=197; Nc=94)	0,0104 (-0,0015 to 0,0224; p=0,088)	$290	$11710	n.a.	1 year	Four one-hour sessions delivered by a nurse over the course of 8 weeks / intervention #10
Robertson W, 2017[28]	Empirical (Ni=56; Nc=59)	0,0009	$770	$818830	n.a.	1 year	Weekly 90-minute sessions consisting of a healthy eating and physical activity workshop for 10-12 weeks / intervention #11
Finkelstein EA, 2014[30]	Modelling	0,011 (0,008 to 0,013)	$377	$34630	Not reported, n.a. implied	Not explicitly reported, 1 year is implied	Low-intensity intervention, not further described as it used meta-analyses / intervention #9
Eriksson MK, 2010[38]	Empirical (Ni=58; Nc=62)	0,08 (EQ5D), 0,20 (EQVAS), 0,07 (SF6D)	$460 (of which $230 is paid by the participant)	$4980 ; $1850 ; $5340 (EQ5D ; EQVAS; SF6D)	3%	3 years	Oral and written information at one group meeting / intervention #18
Sagarra R, 2014[12]	Empirical	0,012119	$1170	$5060	Not re-	4 years	General written and oral information and an

	(Ni=333; Nc=219)				ported		exercise session at base-line and subsequent annual visits / intervention #2
Meads DM, 2014[31]	Modelling	0,06 ; 0,22	112,62 (42,82 incremental) ; 9064,87 (-923,53 incremental)	6906,1 GBP ; cost-saving (924 GBP)	3,50%	1 year; lifetime	Oral or written information on diet, physical activity, and lifestyle change / intervention #12
Smith KJ, 2010[37]	Modelling	0,01	$3420 ($50 incremental)	$4630	3%	3 years	30-minute annual education session and placebo pills / intervention #17
Ahern AL, 2017[29]	Modelling	0,01282 pp	$280	$3490	3,50%	25 years	Given a booklet containing self-help information regarding weight management / intervention #9
Neumann A, 2011[22]	Modelling	0,02 (men ages 30 and 70, women ages 50 and 70) to 0,03 (men age 50, women age 30) pp	$560 year 1 + €270 / year of follow-up	-$36370, -$21830, $39800 (men 30, 50, 70); -$45390, -$30660, $28080 (women 30, 50, 70)	3%	Lifetime	No intervention, not described further / intervention #6
Breeze PR, 2017[24]	Modelling	0,00022 to 0,00073 / million of general population	-$1,2; -$0,3; -$0,3 (if cost is spread over 1 million people)	$480 (or dominant over alternatives)	1,50%	Lifetime	No interventions, rates observed in general population applied / intervention #7
Roberts S, 2018[25]	Modelling	0,23 pp	$940 ; $1480 ; $1550	$4030 (IGT), $9900 (IFG), $10700 (HbA1c)	3,50%	Lifetime	Usual care, not described further / intervention #8
Cobiac L, 2010[35]	Modelling	38 DALYs (whole population); 54 DALYs(whole population)	$250; $210	$128500; $138390	3%	Lifetime	Background trend / intervention #15 and #16
Fuller NR, 2014[36]	Modelling	0,03 pp	$210	savings of $50 ($8350 / QALY in a 5 year perspective)	3,50%	Lifetime	Weight loss advice from a primary care professional at the local GP practice according to Australian, German, and UK guidelines (2013) / intervention #9
Hajizadeh N, 2017[40]	Modelling	0,27 pp (0,12 - 0,37)	$920	Cost-saving ($4430 pp)	5%	Lifetime	NYC DOE pre-k and kindergarten programming / intervention #19

Health system perspective; Societal perspective; Modified societal perspective

3.5. Overview of findings relevant for decision and policy makers

To provide a comprehensive overview of the evidence that may be of particular interest for decision makers in clinical settings, a selection of studies was made to limit the amount of possible sources of variation in cost-effectiveness. To this end, only studies analysing cost-effectiveness in the short- and mid-term, from a health system cost perspective, and using the same discount rate were selected. From this selection, a cost-effectiveness plane was made (Figure 2). A health system perspective includes only direct and indirect medical costs. Where applicable, discount rates used were 3% in all studies included here. By making this selection, possible sources of variation in cost-effectiveness are limited to differences between interventions, the comparator, risk group targeted, and costs of illness included.

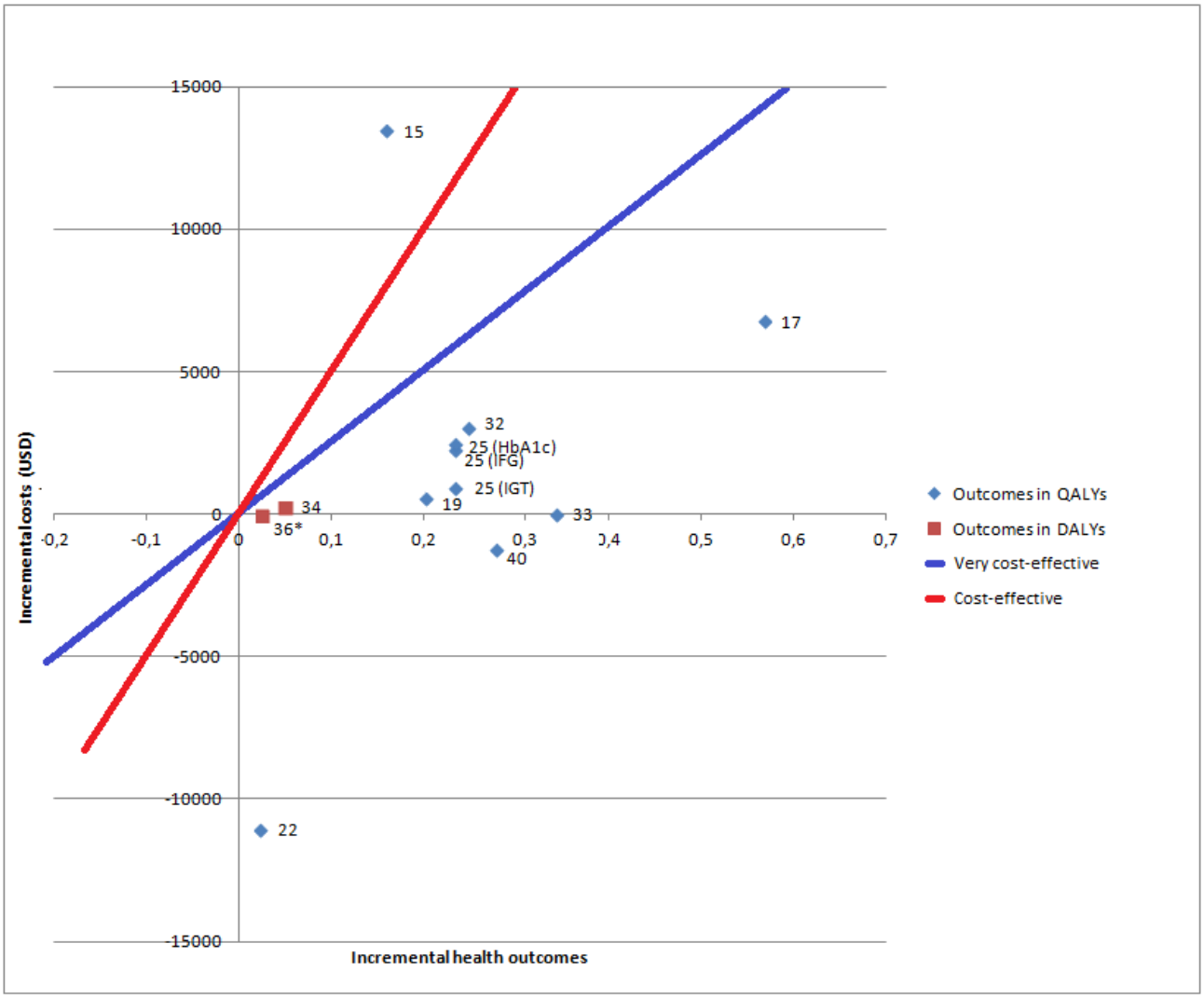


The numbers by the data points represent the respective reference numbers
* QoL measured using the SF-6D questionnaire
** QoL measured using the EQ-VAS questionnaire
***QoL measured using the EQ-5D questionnaire

Figure 2. Short- and mid-term cost-effectiveness of combined lifestyle interventions from a health system perspective.

For policy makers, a cost-effectiveness plane of studies investigating long-term cost-effectiveness from a societal cost perspective is provided in Figure 3. A societal cost perspective includes indirect costs of interventions, such as participant time and travel costs, on top of direct and indirect medical costs. A modified societal perspective does not include costs associated with participant time, but does take into account travel costs.

Except for one study,[15] which employed a time horizon of 30 years, all studies used a lifetime time horizon. All studies included here used either a 3% or a 3.5% discount rate, meaning that the main potential causes for differences in cost-effectiveness between studies are differences between interventions, in assumptions regarding the duration of intervention effects, risk group targeted, the comparator, and variation in costs of illness included.



The numbers by the data points represent the respective reference numbers

* Used a modified societal perspective

Figure 3. Long-term cost-effectiveness of combined lifestyle interventions from a societal perspective.

4. Results from case studies

Of the eight pioneer sites contacted, five project managers agreed to an interview. At the non-pioneer site hospital, managers and initiators of another four projects were interviewed. Three of those projects were grouped together under F1, as they were all interventions targeting children, with the main difference being the age group targeted, and only minor differences in the interventions themselves.

In two of the five pioneer sites, A and B, the local hospital was the initiator, whereas in the other three pioneer sites, C, D, and E, the project was initiated by the municipal government. In the non-pioneer site, F1 and F2, the projects were also initiated by the local hospital.

At sites where the hospital was the initiator, projects concerned the development of a specific combined lifestyle intervention, except for the case of F2, where a web-based application was being developed, which was meant to assist GPs in providing basic dietary advice. All combined lifestyle interventions had been the subject of an effectiveness analysis, though in F1 effectiveness was only studied for one age group, on which the interventions for the other age groups were subsequently based. All interventions achieved a clinically relevant effect. Only at site A had a cost-effectiveness analysis been conducted, although unpublished at the time of writing. A health system perspective would put the intervention in the very cost-effective category, similar to most studies in the systematic review, while from a societal perspective the intervention would be overwhelmingly cost-saving.

Where municipal government was the initiator, projects focused on implementing and developing the national approach for dealing with obesity. This entailed translating principles of combined lifestyle interventions into the existing setting by assigning specific responsibilities to different stakeholders and developing referral schemes. Formal evaluation was being considered at site C, although no concrete plans existed yet. The other sites did not mention any plans for formally evaluating their projects.

Some extra financing was available for pioneer sites, though projects initiated by hospitals were still largely funded by hospital budgets, in addition to healthcare innovation grants, and in the case of site F2 profits from consumers. At site B, some financing was also available through corporate social responsibility budgets of local companies. Projects initiated by municipal governments were mainly financed using their own budgets in addition to the pioneer site financing mentioned before.

Hospitals were principally responsible for developing the intervention at two of the sites where the local hospital was the initiator (A and F). At site B, the hospital had a big role in translating the intervention to a community setting, but was not principally responsible. All of these hospitals conducted scientific research regarding the interventions, and site A and B also handled education of interventionists.

A smaller role was taken by hospitals at sites where the municipal government had initiated the project. At site C and D, hospitals were involved in developing a new referral scheme to determine how primary and secondary care should be coordinated in the case of obesity. At site E, the role of the hospital seemed to be limited to diagnostics of risk factors for comorbidities of obesity.

Universities were involved in development of the intervention at every site where the project was initiated by a hospital. Involvement of universities was not found at any of the sites where the municipal government was the initiator. Municipal governments were involved at all sites where hospitals were the initiator, mainly for finding financing options. Along with insurers and banks, they were also involved in establishing the requirements for building a business case. Municipal health services (GGD), Youth Care, schools, sports associations, GPs, and other primary care providers were involved to determine what their exact role in the interventions should be.

Site	Type	Initiator	Employer interviewee	Development	Formal evaluation	Financing	Role of the hospital	Stakeholders involved in development
A	Pioneer site	Hospital	Hospital	Specific intervention	Cost-effectiveness analysis (€2600*, 0.15 QALYs gained at 3-year follow-up)	Subsidy from the national government for being a pioneer site, provincial subsidies, subsidies from local foundations, innovation fund, hospital budgets	Developing the intervention, responsible for delivery of the intervention (though not by hospital personnel), putting the intervention on the regional and national agendas, educating interventionists	University, independent health coaches, municipal governments, health insurer, community services, GPs, among others
B	Pioneer site	Hospital	Municipal health services	Specific intervention	Cost-effectiveness analysis is being considered (BMI z-score -0.23 (SD 0.32) at 24 months)[41]	Extra financing from the national government for being a pioneer site, hospital budgets, corporate social responsibility budgets of local companies, health equity budgets	Centre of expertise: educating the central healthcare provider, conducting scientific research, translation of the intervention to a community setting	University, municipal health services (GGD), municipal governments, health insurer, community services, schools, sports associations, among others
C	Pioneer site	Municipal government	Municipal health services	Regional approach	Effectiveness analysis is being considered	Extra financing from the national government for being a pioneer site, used for development and central health care provider (Youth Care). Specialist care only on referral	Being involved in development of the referral scheme	Community services, youth clinics, municipal health services (GGD), Youth Care, GPs (employed by a home care provider), schools, among others
D	Pioneer site	Municipal government	Hospital	Regional approach	No formal evaluation	Mainly municipal government	Being involved in development of the referral scheme	Municipal health services, Youth Care, community services, among others
E	Pioneer site	Municipal government	Municipal health services	Regional approach	No formal evaluation	Mainly municipal government	Diagnostics	Municipal health services, Youth Care, community services, GPs, among others
F1	Non-pioneer site	Hospital	Hospital	Specific intervention	Effectiveness analysis (BMI z-score -0.56 (SD 0.54), HRQoL +1.2 psychosocial, +3.5 physical), both at 12-month follow-up)[42]	Healthcare innovation grants, hospital budgets	Developing the intervention, responsible for delivery of the intervention (though not by hospital personnel anymore, hospital personnel did deliver the intervention during the effectiveness study), educating interventionists	University, municipal government, primary care providers, among others
F2	Non-pioneer site	Hospital and university	Hospital and university	Web-based application	No formal evaluation	Healthcare innovation grants, hospital budgets, profits from consumers	Developing the application, performing blood tests, maintaining website and servers	University, a different hospital, regional government, sports association, among others

Table 7. Results from case studies

*From a broad societal perspective the intervention is cost-saving, though the majority of cost-savings goes to the individual

5. Discussion

In this article, a systematic review of the literature on the cost-effectiveness of combined lifestyle interventions has been performed to assess their potential for a positive business case. Additionally, a case study of an approach to dealing with obesity that is being developed in the Netherlands has been conducted, to explore the current role of hospitals in disease prevention and ways of financing such hospital involvement.

From the literature reviewed in this article, it seems that interventions targeted at diabetes prevention achieve greater health outcomes than interventions aimed at preventing or treating obesity. Multiple explanations for this are possible. First, it could be that preventing diabetes simply results in greater health outcomes. Second, it is possible that there are differences between the complications of obesity and diabetes that are included in the calculation of life years gained as a result of the interventions. Third, the majority of studies focusing on obesity prevention and treatment evaluated group interventions, while the majority of articles focusing on diabetes prevention evaluated individual interventions. Group interventions, although generally much less expensive than individual interventions, also seem to generate a much smaller amount of QALYs. Of the 15 articles studying group interventions, 10 reported QALYs gained to be below 0.1, while this was only the case in two out of 14 articles studying individual interventions. QALYs gained between 0.1 and 0.5 were reported in four out of 15 and in nine out of 14 articles for group and individual interventions respectively. In terms of efficiency, though, they are similar.

Of the studies that had other areas of focus, the intervention that seemed most promising was a pre-kindergarten intervention aimed at preventing behavioural problems associated with obesity, high school graduation rates, interaction with the judiciary system, and unemployment. This study was the only one that looked at non-health benefits to society, and provides an indication that behavioural and lifestyle interventions could be more efficient than they seem to be based on most current evidence. Furthermore, only three articles report that interventions are not cost-effective, while 20 reported ICERs in the very cost-effective category, and another six reported interventions to be dominant. In light of this, it is possible that there is some publication bias at play. No statistical method for determining the presence or absence of publication bias in economic evaluations is known to the author, however, so this could be neither confirmed nor refuted.

Data on budget impact in the included articles was also limited. While the health system cost perspective is fairly well studied, societal cost perspectives were used in fewer studies, and when they were used only included participant travel costs as well as their time spent on the intervention. A more complete societal cost perspective would also include costs of sick leave, lost productivity, lost labour years, welfare payments, and other societal costs that are caused by obesity. Including such costs allows estimation of a more complete picture of the impact of interventions on government and also employer budgets.

A cost-effectiveness analysis was performed at one of the pioneer sites, and found the intervention to be dominant over alternatives from a societal perspective, though this was mainly due to large cost-savings going to the individuals receiving the intervention. From a health system perspective, it was found to be very cost-effective. Two other sites had performed effectiveness analyses, both of which found that their interventions produced clinically relevant effects. It is perhaps noteworthy that at all sites that engaged in some form of formal analysis, projects were initiated by hospitals, and universities were involved in the development of interventions.

Where the municipality was the initiator, interest in formal analysis was present, but no concrete plans existed yet. It should be noted here, however, that these projects were still in an early stage of devel-

opment, and details were not yet fully worked out. Due to that, it is possible that the nature of the initiator is not in fact related to conducting a formal evaluation.
The national approach to preventing obesity as well as all interventions developed by hospitals, with the exception of the web-based application, were family-based. In the systematic review, only two economic evaluations of family-based interventions were found, and including those, only three articles were found that studied the application of a combined lifestyle intervention to children. Economic evaluations of the interventions developed and being developed in the Netherlands would thus be a welcome addition to the literature.
Funding of hospital involvement in development of prevention activities was mainly done through hospitals' own budgets and healthcare innovation grants. For such grants to be awarded, however, it is generally required that the project does not run for more than three years, and that the party requesting the grant fronts a substantial part of the costs itself. Other sources of finance included government subsidies for being a pioneer site and local companies' social responsibility budgets. None of these methods provide structural financing, however, nor do they allow hospitals to fully recoup their investment in development of preventive activities.

6. Conclusions and recommendations for further research

Most of the evidence that was found seems to point toward combined lifestyle interventions being very cost-effective (ICER of ≤ $25,000), which would put this type of intervention in the top ~35% most cost-effective interventions of those reported on by Cohen et al,[43] which included interventions of the primary, secondary, and tertiary prevention types.
Based on this, it seems reasonable to assume that it would be possible to build a positive business case for secondary prevention of obesity, as is the case for many other preventive interventions. Despite this, it seems that no structural financing currently exists for hospitals to get involved in developing such preventive interventions in the Netherlands. As the interviews were conducted at pioneer sites, which are meant to experiment with ways, including new financing models, to make healthcare in the Netherlands more sustainable, it seems reasonable to assume that if no sustainable financing was available at these sites, it would be unlikely to be available at other sites as well.
To come to a fair distribution of the financial burden of developing preventive interventions, more research is necessary on the impact of specific interventions on the budgets of different budget holders. A wide scope concerning costs and benefits to be included is needed to achieve this.

7. Limitations

This paper has several limitations. First, as not all pioneer sites were interviewed, it is possible that sustainable methods of financing hospital involvement in disease prevention activities have been overlooked. Second, data extraction was only performed by the first author, and inclusion of articles was only verified on a sample basis by the second author, with the third author being available in case consensus on inclusion could not be reached by the first two authors. Third, quality of the included articles was not assessed using a quality checklist, making it hard to judge the reliability of the evidence included in this review. Fourth, more evidence might have been found if the search terms had specifically included the treatment or prevention of metabolic syndrome or cardiovascular disease. Fifth, the cost-effectiveness thresholds used in this article may not be appropriate for all countries. In the Netherlands, for example, thresholds of <€20,000; €20,001 to €40,000; and €40,000 to €80,000 may be more suitable. Finally, to more thoroughly explore possible ways of financing hospital involvement in developing preventive interventions, it would have been preferable to also interview employees of budget holders other than hospitals and municipal health services.

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6. Hartmann-Boyce J, Johns D, Aveyard P et al. Managing overweight and obese adults: update review. The clinical effectiveness of long-term weight management schemes for adults (Review 1a). Oxford: University of Oxford. 2013. p. 163
7. Van Mastrigt GA, Hiligsmann M, Arts JJ 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 Review of Pharmacoeconomics & Outcomes Research.*2016; 16(6): 689-704. DOI: 10.1080/14737167.2016.1246960
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11. 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): 2518-23.
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13. Herman WH, Edelstein SL, Ratner RE et al. Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. *American Journal of Managed Care*. 2013; 19 (3): 194-202
14. The Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care*. 2013; 35: 723-30.
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17. 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. *Annals of Internal Medicine*. 2005; 142 (5): 323-32
18. Hoerger TJ, Hicks KA, Sorensen SW et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. *Diabetes Care*. 2007; 30 (11): 2874–79.

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36. Fuller NR, Carter H, Schofield D et al. Cost effectiveness of primary care referral to a commercial provider for weight loss treatment, relative to standard care: A modelled lifetime analysis. *International Journal of Obesity*. 2014; 38 (8): 1104-09.
37. Smith KJ, Hsu HE, Roberts MS et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005-2007. 2010; 7 (5): A109.
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42. E Van Hoek. Young Children and Obesity: Development and Evaluation of Family-oriented Treatment [dissertation on the internet]. Wageningen (NL): Wageningen University. [cited 2018 Jul 24]. Available from: http://edepot.wur.nl/356300
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Appendix A – intervention descriptions

Intervention	Details
1	US DPP / DPPOS: 16 one-to-one sessions on diet, physical exercise, and behaviour modification in the first 24 weeks, with monthly contact thereafter, which must be in person at least every two months. During maintenance, 4-6 week group courses are offered. Interventions are provided by case managers with training in nutrition, exercise, or behaviour modification.
2	The intensive intervention group received a structured schedule of 6 h (4 sessions) for 5---15 participants, using specific teaching material. The method was adapted to the available experience, needs and capacity and was based on support, motivation and positive feedback. This program was provided one by one to the participants in the individual modality. The intervention was reinforced with telephone calls, text messages, letters and interviews, scheduled for every 6---8 weeks.
3	Weekly visits for the first month, biweekly for the next 5 months, monthly visits for another 6 months if enough weight loss is achieved. Sessions must last at least 15 minutes and were reimbursed at $25.19 / session. Intervention provided by GP, family practice, internal medicine specialist, obstetrician / gynaecologist, NP, nurse specialist, or physician assistant.
4	Finnish Diabetes Prevention Study: Face-to-face sessions of 30-60 minutes with a dietitian at weeks 0, 1-2, and 5-6, at months 3, 4, 6, and 9, and every three months thereafter. The 7 sessions in the first year had a preset topic, but discussions were individualised. In addition, there were voluntary group sessions, expert lectures, low-fat cooking lessons, visits to local supermarkets, and between-visit phone calls and letters. During the dietitian visits endurance exercise was encouraged, and supervised resistance training was offered. Voluntary group walking and hiking were also organised.
5	One session with a dietitian every 3 months, with the session in the 9th month being a group session. Dietary and physical activity goals were evaluated during visits to the dietitian. An exercise programme was offered, in which participants were stimulated to partake at least 1 hour per week.
6	PREDIAS / SDPP: 8 weekly sessions on physiology, healthy eating, exercise, and motivation in groups of 10, delivered by experts in nutrition and physical exercise, with additional training in diabetes prevention. Participants receive regular (not specified) email and telephone support, monthly newsletters, and quarterly journals on aspects of healthy living.
7	Estimates from meta-analysis of lifestyle interventions
8	The high-intensity lifestyle programme was based on the USDPP [33], and includes 16 one-to-one education sessions delivered by a dietician and 4 exercise sessions supervised by a physical therapist in the first year as well as 12 individual visits and 4 supervised exercise sessions in the second and third year. Further, it includes 1–2 reminder phone calls a month and annual clinical review and blood tests.
9	One year of Weight Watchers (weekly sessions covering nutrition, physical activity, and behaviour change)
10	Multimodal health behaviour modification intervention: 8 sessions in groups of 10-20 covering behaviour change strategies, healthy diet, and physical exercise, with 10 monthly maintenance sessions

11	This intervention places more emphasis on parenting skills, relationship skills and emotional and social development than other UK interventions.
12	Slimming World on Referral: 12 weekly group sessions of 1,5 hours each, covering nutrition, physical activity, and behavioural change. Additionally, a buddy system, as well as telephone and online support are available.
13	Restriction of caloric intake necessary to achieve 10% weight loss under supervision of dietitian, 3 weekly 45-minute exercise sessions supervised by a certified instructor, 2 sessions per month with an exercise therapist, 1-hour cognitive therapy by a psychologist twice per month
14	LEAP: 4 GP consultations (one 40+ minutes, three 20-40 minutes) covering nutrition, physical activity, and lifestyle modification. A 20-page family folder containing additional information was provided for further support.
15	Lighten up: 6 group sessions delivered by trained nurses or allied health professionals and three individual sessions for measurements and personal goal-setting
16	Six months of Weight Watchers (weekly sessions covering nutrition, physical activity, and behaviour change)
17	mDPP: 12 weekly 90-minute group sessions, delivered by a dietitian and exercise therapist who received a 2-day training workshop, to groups of 5-13 participants
18	Björknäs: 3 exercise sessions / week supervised by PT and 5 sessions of diet counseling during the first 3 months, all of which were in groups of 10-13. After the first 3 months, 6 group meetings were organised in the remainder of the first year, 4 in the second, and 2 in the third.
19	ParentCorps aims to buffer the adverse effects of poverty on early child development by engaging and supporting both parents and teachers at school entry. The goal is to promote child self regulation and early learning by increasing positive behaviour support (eg, nurturing parent-child interactions, reinforcement for competencies, proactive strategies), effective behaviour management (eg, limit setting, consistent consequences for misbehaviour), and parent involvement in education (eg. stimulation for learning, book sharing, parent-teacher communication) in home and early childhood education settings.

Appendix B – study settings

Source	Intervention	Setting	Country	Role of hospital staff
DPPRG 2003[11]	1	Hospital	US	Delivery of intervention and data collection
Sagarra R, 2014[12]	2	Primary care	Spain (Catalonia)	Laboratory tests
Herman WH, 2013[13]	1	Hospital	US	Delivery of intervention and data collection
DPPRG, 2013[14]	1	Hospital	US	Delivery of intervention and data collection
Eddy DM, 2005[15]	1	Hospital	US	Same as DPP
Hoerger TJ, 2015[16]	3	Primary care	US	None reported
Herman WH, 2005[17]	1	Hospital	US	Same as DPP
Ackermann RT, 2006[9]	1	Hospital	US	Same as DPP
Hoerger TJ, 2007[18]	1	Hospital	US	Same as DPP
Lindgren P, 2007[19]	4	Primary care	Sweden	None reported
Jacobs-van-der-Bruggen MAM, 2007[20]	5	Primary care	NL	None reported
Schaufler TM, 2010[21]	1	Hospital	Germany	Same as DPP
Neumann A, 2011[22]	6	Unclear	Germany	Unclear
Palmer AJ, 2012[23]	1	Primary care	Australia	Laboratory tests
Breeze PR, 2017[24]	7	Not re-ported	UK	None reported
Roberts S, 2018[25]	8	Primary care	UK	Laboratory tests
Fuller NR, 2013[26]	9	Community	Australia / UK / Germany	None reported
McRobbie H, 2016[27]	10	GPs	UK	None reported
Robertson W, 2017[28]	11	Primary care	UK	None reported
Finkelstein EA, 2014[29]	9	Community	US	None reported
Ahern AL, 2017[30]	9	Primary care	UK	None reported
Meads DM, 2014[31]	12	Community	UK	None reported
Roux L, 2006[32]	13	Unclear	US	None reported
Galani C, 2007[33]	13	Unclear	Switzerland	None reported
Moodie M, 2008[34]	14	Primary care	Australia	None reported
Cobiac L, 2010[35]	15; 16	Primary care and com-munity	Australia	None reported
Fuller NR, 2014[36]	9	Community	Australia	None reported
Smith KJ, 2010[37]	17	Primary care	US	Phlebotomist and lab services
Eriksson MK, 2010[38]	18	Primary care	Sweden	None reported
Bemelmans W, 2008[39]	5	Primary care	NL	None reported
Hajizadeh N, 2017[40]	19	School	US	None reported

Appendix C – excluded articles with reasons

1. Michaud TL, You W, Wilson KE, Su D, McGuire TJ, Almeida FA, Bayer AL, Estabrooks PA. Cost effectiveness and return on investment of a scalable community weight loss intervention. Preventive Medicine. 2017; 105: 295-303. **Intervention does not include personal contact**
2. Makkes S, Van Dongen JM, Renders CM, Van Der Baan-Slootweg OH, Seidell JC, Bosmans JE. Economic evaluation of a intensive inpatient treatments for severely obese children and adolescents. 2017; 10 (5): 458-472. **No control group**
3. Delahanty LM. Weight loss in the prevention and treatment of diabetes. Preventive Medicine. 2017; 104: 120-123. **No economic evaluation**
4. Quattrin T, Cao Y, Paluch RA, Roemmich JN, Ecker MA, Epstein LH. Cost-effectiveness of Family-Based Obesity Treatment. Pediatrics. 2017; 140 (3): **ICERs not reported per QALY or DALY**
5. Saelens BE, Scholtz K, Walters K, Simoni JM, Wright DR. Two Pilot Randomized Trials to Examine Feasibility and Impact of Treated Parents as Peer Interventionists in Family-Based Pediatric Weight Management. Childhood Obesity. 2017; 13 (4): 314-323 **No control group**
6. Robertson W, Fleming J, Kamal A, Hamborg T, Khan KA, Griffiths F, Stewart-Brown S, Stallard N, Petrou S, Simkiss D, Harrison E, Kim SW, Thorogood M. Randomised controlled trial evaluating the effectiveness and cost-effectiveness of 'families for health', a family-based childhood obesity treatment intervention delivered in a community setting for ages 6 to 11 years. Health Technology Assessment. 2017; 27 (1): **duplicate**
7. Schwander B, Hiligsmann M, Nuijten M, Evers S. Systematic review and overview of health economic evaluation models in obesity prevention and therapy. Expert Review of Pharmacoeconomics and Outcomes Research. 2016; 16 (5):561-570. **Used for reference list search**
8. Häußler J, Breyer F. Does diabetes prevention pay for itself? Evaluation of the M.O.B.I.L.I.S. program for obese persons. European Journal of Health Economics. 2016; 17 (4): 379-389. **No full economic evaluation**
9. Morton D, Rankin P, Kent L, Dysinger W. The Complete Health Improvement Program (CHIP): History, Evaluation, and Outcomes. American Journal of Lifestyle Medicine. 2016; 10 (1): 64-73. **No full economic evaluation**
10. Alouki K, Delisle H, Bermúdez-Tamayo C, Johri M. Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies. Journal of Diabetes Research. 2016; 2016. **Used for reference list search**
11. McCombie L, Lean MEJ, Tigbe WW. Cost-effectiveness of obesity treatment. Medicine. 2015; 43 (2): 104-107. **Not the original study**
12. Boyers D, Avenell A, Stewart F, Robertson C, Archibald D, Douglas F, Hoddinott P, Van Teijlingen E. A systematic review of the cost-effectiveness of non-surgical obesity interventions in men. Obesity Research and Clinical Practice. 2015; 9 (4): 310-327. **Used for reference list search**
13. McCollister KE, Tolbert DV, Mishra S, Natale R, Uhlhorn S, Messiah SE. Cost analysis of a childcare center-based intervention to prevent obesity in the preschool years. Journal of Comprehensive Pediatrics. 2015; 6 (2): **No full economic evaluation**
14. Wilson KJ, Brown HS, Bastida E. Cost-Effectiveness of a Community-Based Weight Control Intervention Targeting a Low-Socioeconomic-Status Mexican-Origin Population. Health Promotion Practice. 2015; 16 (1): 101-108. **Follow-up < 1 year**
15. Perri MG, Limacher MC, Von Castel-Roberts K, Daniels MJ, Durning PE, Janicke DM, Bobroff LB, Radcliff TA, Milsom VA, Kim C, Martin AD. Comparative effectiveness of three

doses of weight-loss counseling: Two-year findings from the Rural LITE Trial. Obesity. 2014; 22 (11): 2293-2300. **No full economic evaluation**
16. Hayes A, Lung T, Wen LM, Baur L, Rissel C, Howard K. Economic evaluation of "healthy beginnings" an early childhood intervention to prevent obesity. Obesity. 2014; 22 (7): 1709-1715. **ICER not expressed in cost / QALY or DALY**
17. Flego A, Keating C, Moodie M. Cost-effectiveness of whole-of-community obesity prevention programs: An overview of the evidence. Expert Review of Pharmacoeconomics and Outcomes Research. 2014; 14 (5): 719-727. **Used for reference list search**
18. Spyra A, Riese A, Rychlik RPT. Cost-effectiveness of different programs for weight reduction in obese patients with diabetes [Kosteneffektivität verschiedener Programme zur Gewichtsreduktion bei adipösen Diabetikern]. Gesundheitsokonomie und Qualitatsmanagement. 2014; 19 (2): 79-84. **No comparator**
19. Feldman I, Hellström L, Johansson P. Heterogeneity in cost-effectiveness of lifestyle counseling for metabolic syndrome risk groups -primary care patients in Sweden. Cost Effectiveness and Resource Allocation. 2013; 11 (1) **No description of intervention**
20. Liu X, Li C, Gong H, Cui Z, Fan L, Yu W, Zhang C, Ma J. An economic evaluation for prevention of diabetes mellitus in a developing country: A modelling study. BMC Public Health. 2013; 13 (1) **No behavioural change strategies mentioned**
21. Tsai AG, Wadden TA, Volger S, Sarwer, DB, Vetter M, Kumanyika S, Berkowitz RI, Diewald LK, Perez J, Lavenberg J, Panigrahi ER, Glick HA. Cost-effectiveness of a primary care intervention to treat obesity. International Journal of Obesity. 2013; 37: S31-S37. **Intervention does not meet inclusion criteria (makes use of medication)**
22. Shin J-A, Lee J-H, Kim H-S, Choi Y-H, Cho J-H, Yoon K-H. Prevention of diabetes: A strategic approach for individual patients. Diabetes/Metabolism Research and Reviews. 2012; 28 (SUPPL2): 79-84. **Used for reference list search**
23. John J, Wolfenstetter SB, Wenig CM. An economic perspective on childhood obesity: Recent findings on cost of illness and cost effectiveness of interventions. Nutrition. 2012; 28 (9): 829-839. **Used for reference list search**
24. Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, König H-H. The long-term cost-effectiveness of obesity prevention interventions: Systematic literature review. Obesity Reviews. 2012; 13 (6): 537-553. **Used for reference list search**
25. Griffiths UK, Anigbogu B, Nanchahal K. Economic evaluations of adult weight management interventions: A systematic literature reveiw focusing on methods used for determining health impacts. Applied Health Economics and Health Policy. 2012; 10 (3): 145-162. **Used for reference list search**
26. Hollingworth W, Hawkins J, Lawlor DA, Brown M, Marsh T, Kipping RR. Economic evaluation of lfestyle interventions to treat overweight or obesity in children. International Journal of Obesity. 2012; 36 (4): 559-566. **No specific intervention**
27. Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T, Sampson M. Cost-effectiveness of a lifestyle intervention in preventing Type 2 diabetes. 2011; 27 (4): 275-282. **Insufficient follow-up**
28. Ma S, Frick KD. A simulation of affordability and effectiveness of childhood obesity interventions. Academic Pediatrics. 2011; 11 (4): 342-350. **No specific intervention**
29. Makkes S, Halberstadt J, Renders CM, Bosmans JE, Van Der Baan-Slootweg OH, Seidell JC. Cost-effectiveness of intensive inpatient treatments for severely obese children and adolescents in the Netherlands; A randomized controlled trial (HELIOS). BMC Public Health. 2011; 11 **Only proposal for economic evaluation**

30. Klein A, Chernyak N, Brinks R, Genz J, Icks A. Cost-effectiveness of primary prevention of type 2 diabetes [Kosteneffektivität derPprimärprävention des Typ-2-Diabetes. Ein systematischer Review]. Pravention und Gesundheitsforderung. 2011; 6 (2): 102-110. **Article not in English or Dutch**
31. Loveman E, Frampton GK, Shepherd J, Picot J, Cooper K, Bryant J, Welch K, Clegg A. The clinical effectiveness and costeffectiveness of long-term weight management schemes for adults: A systematic review. Health Technology Assessment. 2011; 15 (2): iii-182. **Used for reference list search**
32. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review. Diabetes Care. 2010; 33 (8): 1872-1894. **Used for reference list search**
33. Saha S, Gerdtham U, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. International Journal of Environmental Research and Public Health. 2010; 7 (8): 3150-3195. **Used for reference list search**
34. Kaplan RM, Atkins CJ, Wilson DK. The cost-utility of diet and exercise interventions in non-insulin-dependent diabetes mellitus. Health Promotion International. 1987; 2 (4): 331-340. **Insufficient description of intervention**
35. Palmer AJ, Valentine WJ, Ray JA. Cost-effectiveness studies of diabetes prevention in high-risk patients. Expert Review of Pharmacoeconomics and Outcomes Research. 2004; 4 (4): 393-402 **Used for reference list search**
36. Burnet DL, Elliott LD, Quinn MT, Plaut AJ, Schwartz MA, Chin MH. Preventing diabetes in the clinical setting. Journal of General Internal Medicine. 2006; 21 (1): 84-93. **Used for reference list search**
37. Finkelstein EA, Khavjou O, Will JC. Cost-effectiveness of WISEWOMAN, a program aimed at reducing heart disease risk among low-income women. Journal of Women's Health. 2006; 15 (4): 379-389. **No economic evaluation**
38. Vijgen SMC, Hoogendoorn M, Baan CA, De Wit GA, Limburg W, Feenstra TL. Cost effectiveness of preventive interventions in type 2 diabetes mellitus: A systematic literature review. PharmacoEconomics. 2006; 24 (5): 425-441. **Used for reference list search**
39. Lauritzen T, Borch-Johnsen K, Sandbæk A. Is prevention of Type-2 diabetes feasible and efficient in primary care?. A systematic PubMed review. Primary Care Diabetes. 2007; 1 (1): 5-11. **Used for reference list search**
40. Icks A, Rathmann W, Haastert B, Gandjour A, Holle R, John J, Giani G. 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. Diabetic Medicine. 2007; 24 (5): 473-480. **No full economic evaluation (no QALYs)**
41. Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, Davies MJ, Khunti K. Different strategies for screening and prevention of type 2 diabetes in adults: Cost effectiveness analysis. BMJ. 2008; 336 (7654): 1180-1184. **Interventions not evaluated individually**
42. Rodríguez CA, López-Valcárcel BG. The economic implications of interventions to prevent obesity [El trasfondo económico de las intervenciones sanitarias en la prevención de la obesidad]. Revista Espanola de Salud Publica. 2009; 83 (1): 25-41. **Article not in English**
43. Jacobs-Van Der Bruggen MAM, Van Baal PH, Hoogenveen RT, Feenstra TL, Briggs AH, Lawson K, Feskens EJM, Baan CA. Cost-effectiveness of lifestyle modification in diabetic patients. Diabetes Care. 2009; 32 (8): 1453-1458. **Treatment of a pre-existing condition other than obesity (diabetes)**
44. Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabe-

tologia. 2010; 53 (5): 875-881. **Intervention description is insufficient to determine whether or not it meets inclusion criteria.**

45. Wang LY, Denniston M, Lee S, Galuska D, Lowry R. Long-term Health and Economic Impact of Preventing and Reducing Overweight and Obesity in Adolescence. Journal of Adolescent Health. 2010; 46 (5): 467-473. **No specific intervention**

Articles from snowballing

1. Hoerger TJ, Crouse WL, Zhuo X, Gregg EW, Albright AL, Zhang P. Medicare's intensive behavioral therapy for obesity: an exploratory cost-effectiveness analysis. American Journal of Preventive Medicine. 2015; 48 (4): 419-425. **Duplicate**
2. Johansson P, Ostenson CG, Hlding AM, Andersson C, Rehnberg C, Tillgren P. A cost-effectiveness analysis of a community-based diabetes prevention program in Sweden. International Journal of Technology Assessment in Health Care. 2009; 25 (3): 350-358. **Public health intervention**
3. Counterweight Project Team, Trueman P. Long-term cost-effectiveness of weight management in primary care. The International Journal of Clinical Practice. 2010; 64 (6): 775-783. DOI: 10.1111/j.1742-1241.2010.02349.x **Duplicate**
4. Segal L, Dalton AC, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. Health Promotion International. 1998; 13 (3): 197-209. **Insufficient description of interventions**
5. Heshka S, Anderson JW, Atkinson RL, Greenway FL, Hill JO, Phinney SD, Kolotkin RL, Miller-Kovach K, Pi-Sunyer FX. Weight loss with self-help compared with a structured commercial program: a randomized trial. Journal of the American Medical Association. 2003; 289 (14): 1792-1798 **No full economic evaluation**
6. 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. **Insufficient description of intervention**
7. Roux L, Kuntz KM, Donaldson C, Goldie SJ. Economic evaluation of weight loss interventions in overweight and obese women. Obesity. 2006; 14 (6): 1093-1096. **Duplicate**
8. 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: 304–321. **ICERs not reported in QALYs or DALYs**
9. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent Type 2 diabetes in Canada. Diabetic Medicine. 2004; 21 (11): 1229-1336 **ICERs not reported in QALYs or DALYs**
10. Gozzoli V, Palmer AJ, Brandt A, Spinas GA. Economic and clinical impact of alternative disease management strategies for secondary prevention in type 2 diabetes in the Swiss setting. Swiss Med Wkly. 2001; 131 (21-22): 303-310. **No multicomponent lifestyle intervention**
11. Eastman RC, Javitt JC, Herman WH et al. Model of Complications of NIDDM: II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes Care 1997; 20 (5): 735-744. **ICERs not reported in QALYs or DALYs**

Appendix D – theoretical framework

To deliver a conceptual framework that can be used for developing hospital based HPDP activities, it will be grounded in theories of business model development, new service development, and decision making logic. A brief outline of the theories used will be provided in this section. First, a description of a number of approaches to business model development will be given. Second, the new service development process will be discussed. Third, theories of decision-making logic will be presented. Finally, these theories will be combined and integrated to form the preliminary version of the conceptual framework.

Business model development

Multiple approaches to developing business models exist, some taking a specific type of business model and providing a method to develop it into a different type of model, e.g. from product to service, [20,21] while others provide a more generally applicable method.[22-25] Hanafizadeh et al. take a Soft Systems Methodology approach, which aims to accommodate diverse views and to facilitate group learning, integrating the three main perspectives on business model development that they identified: the rational positioning view, the evolutionary view, and the cognitive models.[22] Based on that, they develop a long list of questions to guide the development process and evaluate whether predefined goals have been achieved or not. The approach developed by Im and Cho employs morphological analysis (MA) and the fuzzy analytic hierarchy process (FAHP) for development of new business models.[23] They use MA in conjunction with the business model canvas to develop possible alternatives for each business model component, whereafter the combinations of components are assessed by the FAHP, allowing for selection of an optimal business model according to the preference criteria used during the FAHP. França et al. integrate the Framework for Strategic Sustainable Development (FSSD) with the business model canvas, aiming to create a framework for developing environmentally sustainable business models which do not infringe on basic human rights.[24] The way they propose to do this is by collaborating with stakeholders to define certain sustainability principles which will have to be met in the future, and subsequently outlining a plan which will lead to the desirable future state. None of these approaches seem to sufficiently appreciate the dynamic and non-linear nature of the business model development process, however, and assume in large part that a perfect business model can be found and as such do not include any way of fixing a business model that is not performing optimally. This is not so in the framework developed by Vohora et al., though, as it proposes that one can go back to one of the earlier stages in the development process if a business model is found to be deficient in some way, as appropriate for the component that is not functioning well.[25] Moreover, although this framework was developed based on university spin-off companies, the environment of hospitals is characterised by similar factors, such as a lack of resources on the part of the hospital and a lack of entrepreneurial skills on the part of inventors, making commercialisation more difficult. Furthermore, university spin-off companies operate under conflicting objectives of stakeholders, e.g. the university, the academic entrepreneur, the venture's management team, and suppliers of finance. Such conflicting objectives are present in the environment of hospitals as well, and thus this framework is considered to be suitable for this paper.

In their framework, Vohora et al. distinguish five phases: 1) research phase, 2) opportunity framing phase, 3) pre-organisation phase, 4) re-orientation phase, and 5) sustainable returns phase. It must be noted, though, that business model development is a non-linear and recursive process, and that all preceding phases continue during subsequent phases, as illustrated by Figure 1.

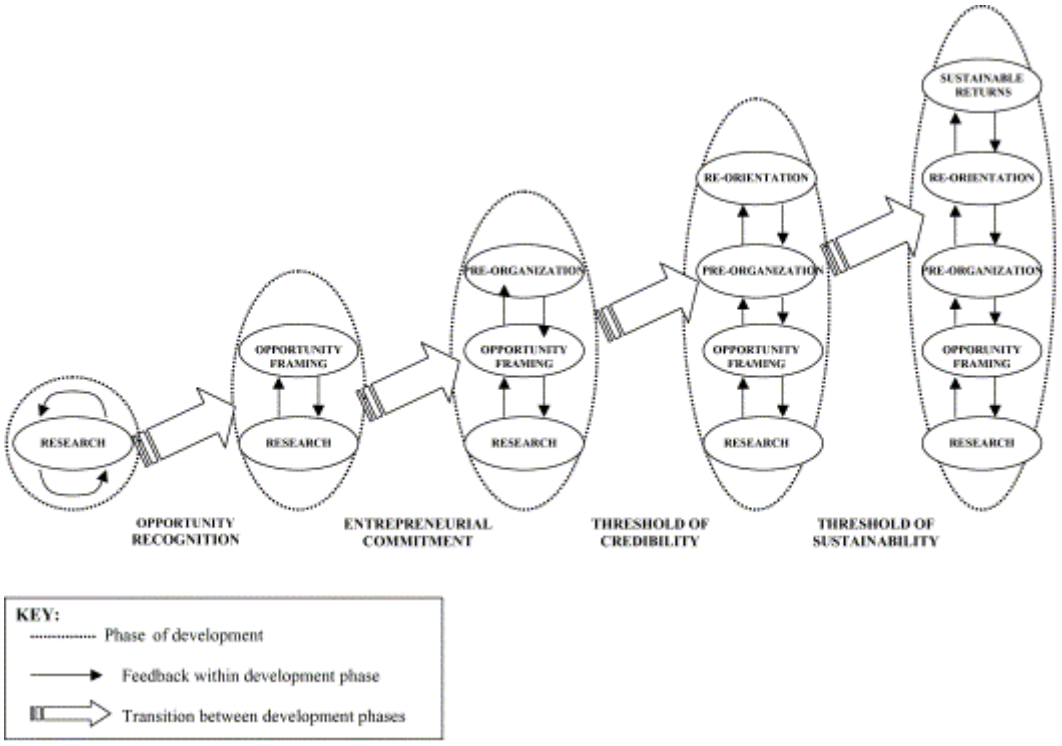

Figure 4. Business model development framework of Vohora et al.[25]

Generally, the research phase is the source of the idea or invention that ends up leading to a business idea. Then, during the opportunity framing phase, further evidence is generated that the idea is viable and target markets are selected. Moreover, it is important to define complementary resources that will be necessary in the future, as well as how to access or acquire those resources, and to assess the opportunity thus framed in cooperation with customers, financiers, and industry incumbents.
In the pre-organisation phase, one or multiple opportunities are selected and strategic decisions regarding access to, development, and acquisition of resources needed in both the present and the future, as identified in the opportunity framing phase, are taken. The re-orientation phase is where first attempts at generating revenue are made. While doing so, continuous identification, recruitment, integration, and reconfiguration of resources becomes necessary. This reconfiguration of resources most often results in changes to the key activities, customer segments, and revenue model.
In the sustainable returns phase, technological and market uncertainty are reduced to such a degree that changes to the business model are scarcely necessary, allowing the business to focus on generating revenue. Even in this phase, though, it is important to take a dynamic approach to the business model, and allow for enough flexibility to respond to changes in the environment as needed.

New service development

The new service development cycle presented by Johnson et al., as illustrated below, goes through four steps in a non-linear process: design, analysis, development, and full launch.[26] It can be seen as taking place within the business development framework of Vohora et al.[25] They describe the first two stages, design and analysis, as the planning stage, wherein things such as market viability and internal resources and capabilities are considered. These first two stages, then, as well as the activities performed within them, would be a good fit for the opportunity framing and pre-organisation phases of Vohora et al.'s business model development framework. Johnson et al. refer to the following two stages, development and full launch, as the execution phase, in which the service delivery system is designed. They also emphasise the importance of cross-functional collaboration and use of enablers in

this phase. As such, the execution phase overlaps mainly with the re-orientation and sustainability phases of Vohora et al.'s framework. Integrating these two frameworks provides detailed guidance on what activities should take place at what time, while not sacrificing much in the way of comprehensiveness.

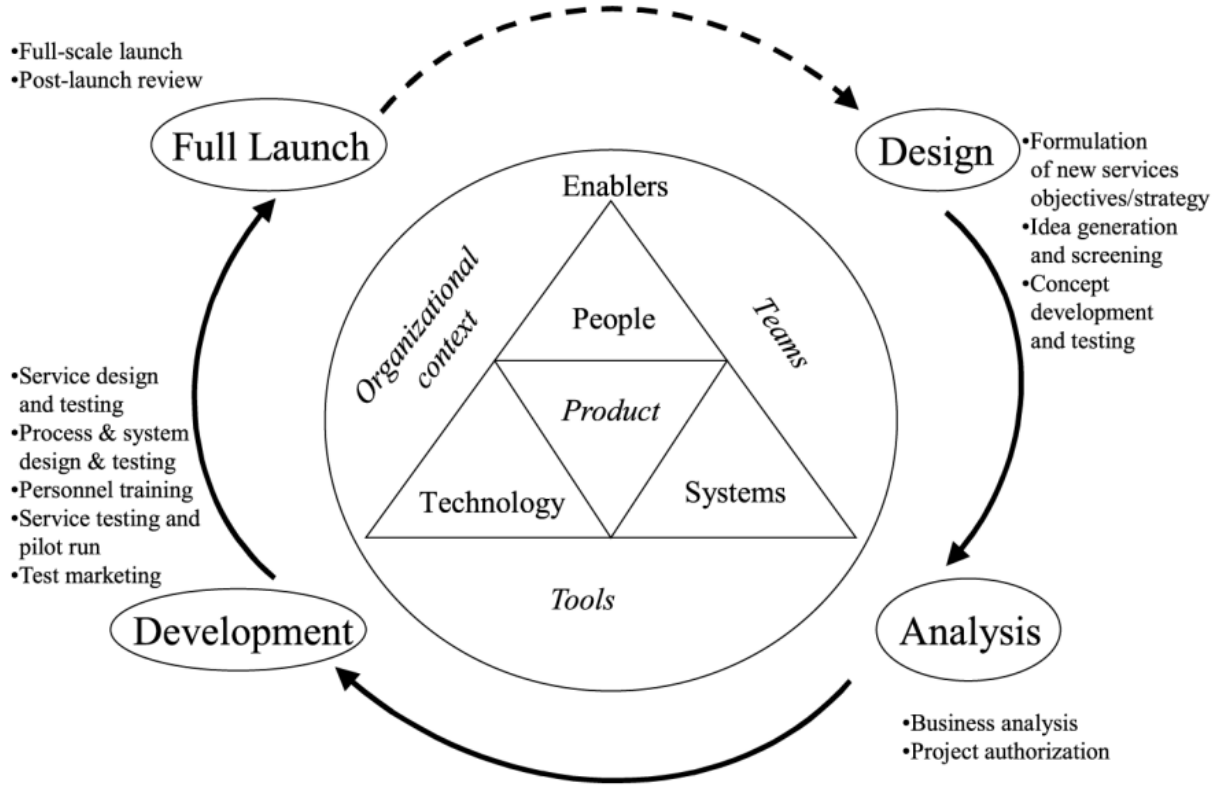

Figure 5. Service development cycle

Decision making logics

Recent research has made a connection between the business model components and the dominant decision-making logics that are employed in changing each of them.[27] A distinction is made based on the extent to which planning is emphasised, resulting in the decision-making logics effectuation and causal logic. While effectuation places little importance on planning and more on flexibility, mainly utilising an array of creativity techniques, causal logic uses methods of analysis, prediction, and planning to reach a certain goal.[28]

Furthermore, where causal logic takes a specific goal as given, and tries to find the most efficient way of realising that goal, effectual logic starts from a set of means, and constructs a variety of goals that could be accomplished given those constraints. Reymen et al.[27] found that effectual logic is the dominant decision-making logic used by USOs mainly to reduce technological and market uncertainty, by experimenting with different value propositions and market segments. This reduction in uncertainty subsequently results in a shift in decision-making logics to a dominance of causal logic, which would be applied to define the remaining business model components, as presented by Osterwalder.[29] Understanding of these decision making logics should be helpful in deciding what sort of technique to use to solve any given problem that arises during the development of a business model.

Integrated conceptual framework

In this section, a more detailed description will be provided of what activities need to be performed in each phase of business model development.

Research phase

Starting off with the research phase, it may not be obvious what proactive actions could be taken here, since generally hospitals that conduct research will always have some research going on. However, serendipitous discovery of opportunities may not be desirable if a hospital wants to adopt a more structural approach to HPDP. Thus, in this phase, if one were to adopt a perspective of causal logic, it would be possible to find opportunities by conducting PESTEL analyses or interviewing stakeholders to determine what demands exist in the market. Once market demands are identified, an approach to meeting these demands can be planned out in the following phases of business model development. On the other hand, if one would adopt a perspective of effectual logic, a set of constraints could be found by performing a SWOT analysis and identifying both internally and externally available resources. From these constraints, one could work towards the development of HPDP activities through creatively configurating available resources.

Opportunity framing phase

In either case, multiple opportunities will likely be identified, at which point the opportunity framing phase is reached. In this phase, if the opportunities stem from research or were found using the causal logic approach, it will be necessary to define resources that will be necessary to realise said opportunities, as well as to define how to acquire them. This is not needed if the effectual approach was taken, since that takes available resources as a set of constraints, and does not attempt to acquire new resources. Furthermore, for all approaches, design of the service should be started in this phase of development, focusing on producing alternatives for the Key Activities, Channels, Revenue Streams, and Cost Structure components of the Business Model Canvas[29]. As a result, an early version of all components of the business models, except for Customer Relations, will exist. Based on this, it will be useful to discuss the opportunities with relevant stakeholders, such as clients, partners, financiers, regulators, etc, so that appropriateness of the business model components can be gauged at an early stage. Another key activity in this phase is the generation of evidence for the effectiveness and cost-effectiveness of interventions, since Cost-Effectiveness Analysis (CEA) and Budget Impact Analysis (BIA) are increasingly demanded by reimbursement authorities as part of listing submissions.[30] Such analyses would be useful, then, for discussions with financiers regarding suitable financing options. An in-depth discussion on such options will be presented the next section. Generating evidence of sufficient quality for use in CEAs and BIAs will take multiple years, however, so doing that for all opportunities would be a rather costly endeavour. Therefore, it might be preferable if some agreed upon method existed for separating the wheat from the chaff in a smaller timeframe. An early attempt at such a method has been made by Fazal et al.,[31] however, owing to the fact that it is still very recent, universal consensus among health professionals and healthcare payors is unlikely to exist at this point. Nonetheless, it could be used as a basis for discussions between and among these groups so that a method for early identification of promising HPDP activities may exist eventually. Until then, it will be necessary to carry out a full cost-effectiveness analysis (CEA) for all opportunities, so that those interventions that are most likely to be cost-effective may be prioritised.

Pre-organisation phase

Based on the results of the analyses performed and feedback collected from stakeholders during the opportunity framing phase, one or multiple opportunities can be selected for further development. This selection marks the start of the pre-organisation phase. During this phase, it becomes necessary to take strategic decisions regarding access to, acquisition, and development of resources that are or will be needed for the selected opportunities. For example, it needs to be decided whether existing staff should be trained to deliver the new intervention, new staff who already have the requisite skills should be hired, or that it should be outsourced to independent providers. Similar decisions will need

to be made for other necessary resources. At the same time, service design, as well as process and system design will be ongoing, as in the development stage of the new service development cycle.

Re-orientation phase

When all the relevant strategic decisions have been made, first attempts can be made at commercialisation of the HPDP activities that are under development, indicating that the re-orientation phase has been reached. In this phase, the decisions made in the pre-organisation phase will have to be put into practice, so that testing of the service design can begin, as in the development stage of the new service development cycle. Any areas for improvement should be identified during this phase to prepare for full launch. To do so, once again an approach of causal logic or effectuation can be chosen. As long as it is established that an interest in the value proposition exists, and the appropriate market segment is being targeted, a perspective of causal logic should be taken.[27] Through learning processes that stem from interactions with networks and stakeholders, as well as from service testing, components of the business model that are not working well can be identified. With that information, existing resources can be reconfigured, or, if necessary, an approach to develop, acquire, or access new resources can be worked out. If new resources do turn out to be needed, that basically means that the opportunity framing phase, where resources are identified, and the pre-organisation phase, where strategic decisions regarding resources are made, have to be gone through again. In the case that either the value proposition or the market segment appear to be inappropriate, an effectual perspective should be taken to find other options for these components which would be achievable with the already available resources. If this does not deliver any promising results, it should be considered to terminate the project and start over from the research phase.

Sustainable returns phase

Once uncertainty is perceived to have been reduced sufficiently, the project can enter full launch, and as such the sustainable returns phase of the business model development process is reached. During this phase major changes to the business model should rarely be necessary, though a vigilant attitude must be maintained to make sure that it keeps functioning well.