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A SYSTEMATIC REVIEW OF THE COST-EFFECTIVENESS OF NON-SURGICAL OBESITY INTERVENTIONS IN MEN

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Abbreviations

BMI:	Body Mass Index
UK:	United Kingdom
USA:	United States of America
QALY:	Quality Adjusted Life Year
NIHR:	National Institute for Health Research
HTA:	Health Technology Assessment
NHS:	National Health Service
OECD:	Organization for Economic Co-Operation and Development
CEA:	Cost-Effectiveness Analysis
CUA:	Cost-Utility Analysis
ICER:	Incremental Cost-Effectiveness Ratio
NICE:	National Institute for Health and Care Excellence
EUnetHTA:	European Network for Health Technology Assessment
CADTH:	Canadian Agency for Drugs and Technologies in Health
RCT:	Randomized Controlled Trial
GP:	General Practitioner
IHD:	Ischaemic Heart Disease
WTP:	Willingness To Pay
M.O.B.I.L.I.S	Multizentrisch Organisierte Bewegungsorientierte Initiative zur Lebensstiländerung In Selbstverantwortung (translated from German as a Multi-centre movement oriented initiative for lifestyle change through self-responsibility)
DGE	Deutsche Gesellschaft für Ernählung (translated from German as the German Society for Nutrition)
XENDOS:	XENical in the prevention of Diabetes in Obese Subjects
HbA1c:	Haemoglobin A1c
IGT:	Impaired Glucose Tolerance
CEAC:	Cost-Effectiveness Acceptability Curve

CHF:	Swiss Francs
GBP:	Great British Pounds
FFIT:	Football Fans In Training
UKPDS:	United Kingdom Prevention of Diabetes Study

Abstract:

Background:

Increasing obesity related health conditions have a substantial burden on population health and healthcare spending. Obesity may have a sex-specific impact on disease development, men and women may respond differently to interventions, and there may be sex-specific differences to the cost-effectiveness of interventions to address obesity. There is no clear indication of cost-effective treatments for men.

Methods:

This systematic review summarises the literature reporting the cost-effectiveness of non-surgical weight-management interventions for men. Studies were quality assessed against a checklist for appraising decision modelling studies.

Results:

Although none of the included studies explicitly set out to determine the cost-effectiveness of treatment for men, seven studies reported results for subgroups of men. Interventions were grouped into lifestyle interventions (five studies) and Orlistat (two studies). The retrieved studies showed promising evidence of cost-effectiveness, especially when interventions were targeted at high-risk groups, such as those with impaired glucose tolerance. There appears to be some sex-specific elements to cost-effectiveness, however, there were no clear trends or indications of what may be contributing to this.

Conclusion:

The economic evidence was highly uncertain, and limited by variable methodological quality of the included studies. It was therefore not possible to draw strong conclusions on cost-effectiveness. Future studies are required to demonstrate the cost-effectiveness of interventions specifically targeted towards weight loss for men.

INTRODUCTION:

Overweight and obesity are significant population health concerns. US data from 2007-2010 show that based on having a BMI (Body Mass Index) ≥ 30kg/m^2, 34.4% of men and 36.1% of women were obese [1]. In England in 2011, 24% of men and 26% of women were obese, however 65% of men and 58% of women were overweight [2]. Projections from the UK Foresight report [3] show that men will overtake women for obesity (47% and 36% respectively by 2025). However, morbid obesity (BMI ≥ 40kg/m^2) tends to be less prevalent in men than women [2] [4]. Worldwide, there is a substantial sex and geographical effect to obesity trends. Increases in BMI for men have generally tended to be greatest in high income countries (especially USA and UK). However, for women, increases in BMI have been greatest in southern and central Latin American countries [5]. Reasons for the sex and country specific interactions in trends are not immediately clear, however the data re-enforce the importance of developing interventions targeted by region and sex.

Obesity in men is a risk factor for a very wide range of diseases impacting on health and quality of life. Most notably are the increased risks of cardiovascular disease, diabetes and cancers which can be attributed in part to obesity. Men with BMI ≥ 30kg/m^2 and waist circumference ≥ 102cm have an increased risk of at least one symptom of impaired physical, psychological or sexual function, and these symptoms are also more likely in men with raised waist circumference (≥ 102 cm), but BMI < 30kg/m^2 [6] [7] . Evidence is clear that for the whole population, obesity related health conditions are responsible for a significant proportion of national health spending. This economic burden is only likely to increase over time, given increasing obesity rates worldwide. If past trends continue, there could be 65 million more obese people in the US, and 11 million more in the UK, by 2030 [8]. The associated combined medical costs of treating preventable diseases attributed to rising obesity trends were estimated to increase by $48-$66 billion per year and by £1.9-£2 billion per year in the United States of America (USA) and UK by 2030, respectively, representing at least2% of UK annual healthcare spending [8].

Furthermore, based on these trends, the UK could lose 6,300,000 Quality Adjusted Life Years (QALYs) by 2030 as a result of the rising obesity problem [8]. The same study predicted that a 1% reduction in

BMI for every adult, based on baseline values could save 3,195,000 QALYs by 2030 [8]. Despite some uncertainty in the literature regarding the assumptions underpinning the future trends in obesity worldwide [9] [10], there is general consensus that obesity rates will continue to increase into the near future, with significant impact, not only on health care costs, but also on population health, quality of life and the social, economic and emotional costs to those individuals affected.

The burden of obesity on healthcare and wider economic costs has motivated the evaluation of clinical effectiveness and cost-effectiveness of a range of treatment strategies, including drug therapy, surgery, diet and physical activity, all of which have been shown to have varying degrees of success, regardless of sex, in modifying the obesity problem. Recent systematic reviews have summarized the current literature on the long term cost-effectiveness of obesity prevention interventions generally [11], and the cost-effectiveness of therapeutic interventions [12].

This purpose of this article is to report an updated systematic review of the cost-effectiveness of non-surgical treatments in the management of obesity in men and to summarize the literature on this important topic. The original work formed part of a larger research project funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) program [13], which reviewed the clinical and cost-effectiveness and qualitative literature on obesity management for men, since men are much less likely to take part in trials or evaluations of weight loss interventions [14]. This report [13] found clear evidence that policy makers should take account of sex and gender differences when designing services for obesity management, and that design differences between men and women may influence uptake, effectiveness, dropout rates and costs.

This article reports the costs, outcomes and cost-effectiveness of a range of strategies for the management of obesity in adult men, with an appropriate quality assessment of the included studies, based on best practice economic evaluation methodology.

METHODS:

Identification of studies:

An extensive and highly sensitive search strategy using appropriate subject headings and text word terms was developed to identify alternative strategies for weight loss, with a distinct and interpretable focus on strategies for the management of obesity in adult men [13]. The literature search included both ongoing studies and grey literature. Databases searched were: MEDLINE (1946 –October 2014); MEDLINE-in-Process (24th October 2014); Embase (1974 – October 2014); Health Management Information Consortium (1979 – October 2014); National Health Service (NHS) Economic Evaluations Database; Cost-effectiveness Analysis Registry; Research Papers in Economics (all searched up to October 2014). No language restrictions were imposed, however the search was limited to studies published post 1990. Full details of the search strategy used for the MEDLINE and Embase databases are presented in Appendix 1 to the paper. Further details of the search strategies for other databases are available from the authors on request.

Inclusion and exclusion criteria:

Economic evaluations, with full description of economic methods and results conducted alongside randomized trials and *de novo* decision analytical models that comparatively analyzed costs and outcomes in an economic evaluation framework were included. Methodological papers, review papers, cost of illness papers and studies which did not conduct a formal comparison of costs and outcomes (i.e. those studies which did not conduct a full economic evaluation) were excluded. A full economic evaluation was defined as a cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis or cost-minimisation analysis framework. We excluded studies from this review which reported limited cost-effectiveness outcomes, as the primary purpose of the publication was to present clinical results. Such studies were excluded as they would not present methods and / or results in sufficient detail, and we could not quality assess the study.

Studies were included if they reported results either wholly or for a sub-group of men (mean or median age of 16 years or over, with no upper age limit). Studies particularly examining men with obesity related to psychotropic medication, diagnosed eating disorder or with learning disabilities were excluded. The following interventions were included: Orlistat (but not Sibutramine or Rimonabant, which no longer have European Medicines Agency licenses); diet; physical activity; behaviour change relating to weight loss; or combinations of any of these. Complementary therapies, surgical procedures and other medications were excluded. Economic evaluation studies were only included if their main aim was to evaluate the cost-effectiveness of weight loss interventions. Studies examining combinations of interventions, other than the combinations outlined above, were not included. For example, we did not include interventions combining smoking cessation with weight loss. Studies were therefore deemed fit for inclusion in the review if they were full economic evaluations producing weight loss, where results were reported solely or for sub-groups of men.

<u>Study selection, data extraction and reporting</u>

Data extraction was undertaken by the project health economist (DB). Data extraction forms were checked by a second member of the review team (AA) for consistency and accuracy. The data extraction process focused on two key areas: (i) the results of the economic evaluations in terms of estimates of costs and effects; and (ii) the methods used to derive the results. Summary data from each study are reported and a narrative discussion is presented. The aim of the narrative is to identify common results, methodological strengths and weaknesses across interventions and to inform future applied and methodological research. Due to the wide variation in reported currencies and costing years, we have inflated costs from the study year of reporting to 2014 values using appropriate inflation indices for each individual country [15] [16], and converted to UK £, using purchasing parity indices provided by the Organization for Economic Co-operation and Development (OECD) for non-UK studies[17]. The presentation of data from the studies in common year and currency estimates is to facilitate a discussion of the results across broad intervention groups, but is not intended in any way to represent a formal quantitative synthesis of the data. All included studies were quality assessed using the Philipp's checklist for decision modelling in economic evaluations [18].

Reporting of economic evaluations:

Included studies report costs, outcomes and synthesize these estimates within a formal economic evaluation framework. Economic evaluations are based on the principles of scarcity and choice. Many healthcare interventions may improve patient outcomes. However, healthcare resources are scarce, and so decision makers have to make choices on the best way to spend their limited health budgets. Economic evaluation is a way in which we can attempt to allocate money to health care interventions in the most efficient way possible, gaining maximum health outcome with restricted investment. There are two main methods of economic evaluation which have been included in this review, namely cost-effectiveness analyses (CEA) and cost-utility analyses (CUA). Both present a comparison of the additional costs of a new intervention with the improvement in outcomes. Results are usually presented in terms of the Incremental Cost-Effectiveness Ratio (ICER), which is simply given as [(Cost of new intervention – Cost of standard) / (Outcomes of new intervention – outcomes of standard)]. Lower values of the ICER are preferred as they offer better value for money. The difference between CEA and CUA lies in how outcomes are measured. For CEA, outcomes are measured in terms of natural units, such as life years gained, reduced cases of diabetes etc. For CUA, outcomes are typically measured in terms of QALYs, which combine benefits in reduced mortality with a measure of quality of life. QALYs are the preferred outcome measure for decision making bodies such as the National Institute for Health & Care Excellence (NICE), the European Network for technology assessment (EUnetHTA), the Canadian Agency for Drugs and Technology in Health (CADTH) and other decision making bodies as they provide a common metric for the comparison of new interventions across the health services. Each country and decision making body will have their own criteria for recommending interventions as cost-effective. For example, NICE typically recommend interventions for reimbursement in the UK if the cost of achieving a one unit improvement in QALYs is less than £30,000 ((i.e. an ICER < £30,000 per QALY) [19]. Further, if an intervention which improves QALYs is found to also generate long term cost savings, for example if cost savings achieved from reducing long term incidence of coronary heart disease were greater than the costs of intervening now, then this offers an even stronger case for cost-effectiveness and is reported as being cost saving or the “dominant” intervention in the analysis. As obesity is a predictor for the development of chronic health conditions, we are interested not only in short term outcomes from randomized controlled trials (RCTs), but also in the longer-term costs and outcomes associated with differential risks of developing chronic diseases such as diabetes and heart disease. It is therefore common economic evaluation practice to extrapolate short-term outcomes from clinical trials (e.g. blood pressure, cholesterol levels, BMI) to longer term health outcomes, such as risk of disease and mortality as well as the healthcare costs associated with such diseases over a patient’s lifetime. In order to make these predictions, economic evaluations typically use decision analytical models, often Markov models, which estimate future costs and outcomes attributable to an intervention based on the probability of developing diseases into the future. This extrapolation of costs and outcomes forms an important tool in economists’ evaluation of healthcare interventions.

RESULTS:

Original searches of the literature were conducted to 2012 and updated to 2014. In total, the primary searches identified 2,333 potentially relevant titles and abstracts, 90 studies were selected for full text retrieval to further assess their eligibility criteria for our study. Upon reading all full text papers, a total of seven studies [20] [21] [22] [23] [24] [25] [26] were deemed to meet our inclusion criteria and were formally included for the review and quality assessment. A flow chart of included studies from the original review is available from the original project report [13]. Due to study heterogeneity, we did not undertake formal meta-analysis of results. Therefore, a narrative discussion of the cost-effectiveness results is presented with included studies grouped into two categories: 1) studies that focus on lifestyle interventions (5 studies [20] [21] [23] [25] [26]) and 2) studies that focus on Orlistat pharmacotherapy (2 studies [22] [24]). In addition to the included studies, we retrieved two further clinical guideline documents [27] [28] from NICE, the first of which briefly discusses sex-specific issues in the cost-effectiveness or Orlistat [27], with the latter guidance relating to the management of overweight and obese adults through lifestyle weight management services [28]. Detailed study characteristics, interventions and comparator treatments evaluated in the studies are presented in Table 1 whilst the main cost-effectiveness results are presented in Table 2.

Lifestyle interventions:

Segal and colleagues [21] found that a group diet and physical activity behavioural modification intervention for men, was both cost saving to health services and also more effective than providing no routine care, thus demonstrating favourable cost-effectiveness results. The intervention was most cost-effective when restricted to those at greatest risk of type II diabetes (i.e. those with impaired glucose tolerance). The study conclusions were robust to plausible variation in the treatment success rate of the programme.

Olsen and colleagues [23] found that General Practitioner (GP) counselling was more cost-effective than dietician provided counselling to encourage weight loss and reduce the risk of developing ischaemic heart disease (IHD) or death. It should be noted however that there were important differences in the content of the advice provided to the different groups. GP advice included general broad lifestyle advice and the delivery of commercially available information on healthy diet, whereas dietician provided advice was more focussed and concentrated on the principles of good nutrition. The authors speculate that favourable results for GP consultations may be driven by the additional general health advice which they routinely provided. Despite the cost-effectiveness results favouring GP over dietician support, the authors conclude that the role of the dietician should not be discounted, especially given health care provider constraints in practice.

Galani and colleagues [20] found that a structured lifestyle intervention (including regular dietician visits and supervised exercise sessions), delivered to overweight and obese adults over the course of three years was dominant (cost saving and more effective) for borderline obese and was also highly cost-effective for overweight and obese men, with low ICERs, offering excellent value for money to health services providers. Results were also robust to sensitivity analyses, adding to the strength of the study's conclusions.

Miners and colleagues [25] evaluated an e-learning device with tailored feedback to participants over a lifetime horizon using a discrete event simulation model, but did not find evidence to prove cost-effectiveness compared to a conventional care package including dietary and physical exercise advice. The results were highly sensitive to the cost of providing the online programme and the authors note that their conclusions should not be generalized to all web-based interventions.
Spyra and colleagues [26] evaluated four alternative lifestyle interventions against a 'do nothing' approach. Three commercially provided programs, involving specially trained providers, for German social health insurance funds and therapeutic nihilism (with no medical or specialist intervention) were compared. A two phase programme of protein rich meal replacement followed by a maintenance phase with medically controlled long term specialist care was found to be the most cost-effective treatment

option. Specific intervention details were however not provided rendering it difficult to assess the applicability or generalizability of the results.

NICE Guidance on Lifestyle Interventions:

NICE have also recently issued guidance on lifestyle weight management for overweight and obese adults [28], which included a review of the literature on cost-effectiveness and additional sex specific modelling of longer term costs and effects. The results of the review showed lifestyle interventions to be cost-effective, but studies were of variable quality. The additional modelling carried out showed that lifestyle interventions costing £100 per person for a 12 week programme, or costing £200 for a 24 week programme would be cost-effective if the amount of weight lost is maintained for life. Whilst sex was found to be an influencing factor, it was not a major driver of cost-effectiveness results. However, the model was highly sensitive to the assumptions surrounding maintenance of weight loss, showing that if weight was regained over 2 years or less, such interventions would no longer be cost-effective. The length of required weight loss maintenance required for cost-effectiveness was less for older people. Maintenance of weight loss over time is a critical driver of cost-effectiveness, and further research is required to identify the best evidence for populating economic models.

Drug treatment with Orlistat:

Two studies estimated the cost-effectiveness of Orlistat in overweight and obese men. Ianazzo and colleagues [22] reported a cost-utility analysis of Orlistat (120mg, three times daily), over a four year time period in addition to a lifestyle intervention (dietary and physical exercise components) for the prevention of type 2 diabetes, in an Italian obese population. There was no clear evidence that Orlistat was cost-effective in overweight and obese men. However, the results were highly sensitive to the level of risk of developing diabetes. Therefore, the authors concluded that if the drug was targeted at a high risk group, then the treatment was much more likely to be a cost-effective use of healthcare resources.

Maetzel and colleagues [24] evaluated Orlistat 120mg taken three times daily for only one year in addition to standard treatment guidelines for type 2 diabetes (an 11 year diabetes treatment programme) in a US healthcare setting. Standard diabetes care included pharmacotherapy (e.g. metformin) and weight management in the form of dietary and physical activity advice. Orlistat was found to be cost-effective. However, the authors note that conclusions were highly sensitive to the duration of treatment effect, with greater duration of effect greatly improving cost-effectiveness. Observational data to support long term use of Orlistat in this population are needed to validate the results of the study.

National level Guidance on the use of Orlistat:

Our review identified one clinical guideline document which evaluated the cost-effectiveness of Orlistat, and presented data separately for men and women. The National Institute for health and Care Excellence (NICE), the UK's decision making body for the recommendation of treatments for reimbursement on the NHS, has issued obesity guidelines (clinical guideline number 43) [27], which included an update of original NICE guidance on Orlistat (Technology Appraisal number 22) [34]. Additional modelling work was undertaken to estimate sex-specific quality of life weights to inform QALY calculations, and for use in subsequent economic modelling exercises. Sensitivity analyses reported QALY and cost per QALY outcomes separately for men, based on available effectiveness (weight loss) and cost data for Orlistat. There was no evidence of differing cost-effectiveness for men and women based on 12 months' treatment with Orlistat, with ICERs well below a commonly acceptable willingness to pay of £20,000 per QALY gained [19]. Differences between men and women appear to be more pronounced when evaluating longer term Orlistat treatment over 48 months. Over this longer treatment period, the base case analysis reports higher cost per QALY for men (£29,089) compared to women (£26,917). Within this analysis, for men, the data suggest that the greater the initial BMI, the more cost-effective Orlistat is (ICER = £29,920; BMI = 38kg/m^2), with the ICER increasing to £33,134 when initial BMI is 30kg/m^2. The converse appears to be true for women: ICER = £30,155 for an initial BMI = 38kg/m2; ICER = £23,982 for an initial BMI = 30kg/m^2. The results show that for the comparison of 48 vs. 12 months' treatment with Orlistat, cost-effectiveness is dependent upon a number of factors, including sex, baseline BMI, weight trend without Orlistat, and weight regain after treatment discontinuation. The conclusion of the evaluation was that NICE could not recommend 48 months of treatment, given the uncertainty in the ICER presented. This appears to be the only publicly available guidance internationally which highlights the cost-effectiveness of Orlistat specifically for men.

Quality assessment of the included studies:

The results of all the included studies should be interpreted in light of highly variable methodological quality. All included studies were formally quality assessed according to the Phillip's critique for economic evaluations [18]. Five studies used Markov models to extrapolate short term outcomes over a longer time horizon and estimate cost-effectiveness [20] [21] [22] [24] [26], one used a discrete event simulation model [25] to compare the time to development of obesity related complications and oneused Cox regression modelling to estimate time to death as a measure of effectiveness [23]. However, the latter only projected long term outcomes, not costs. This is an important omission from economic studies as cost implications to health services are likely to occur far into the future, through differing risks of developing health related complications and requiring expensive hospital care. The disease states included in the modelling process varied depending on the study. The most common disease states modelled were heart disease and diabetes. Given the many health related complications associated with obesity and their chronic nature, Markov models and or discrete event simulation models, which extrapolate both costs and outcomes over a long time horizon, including for diseases other than heart disease and diabetes such as cancers and osteoarthritis, could be argued to give the most appropriate estimate of cost-effectiveness.

While more sophisticated models are often preferred, it is also important to consider the underlying processes, quality of the data used to populate the model and the underlying assumptions used to estimate cost-effectiveness. Data used within the models were generally well described and clearly referenced, though there is little evidence of formal systematic searching for data to populate the models. Methods used to synthesize data from the literature to estimate model treatment effects were poorly described. Only two studies detailed the meta-analysis carried out [20] [25].

The costing perspective was described in all studies. The most common perspective was that of the health services, though two studies stated a societal perspective [20] [22] and one a social health insurance perspective [26]. Intervention costs were included for all studies, and downstream costs to health services included in six out of the seven. Despite their inclusion in the evaluations, the calculation of intervention and downstream costs was not always thoroughly reported and prevented reproducibility of the results. Where appropriate, costs were discounted to their present day values, though only three studies tested the impact of varying discount rates on cost-effectiveness outcomes in sensitivity analyses [20] [24] [25].

Effectiveness data used in the models were, for the most part, based on weight loss which was used to predict clinical outcomes such as cholesterol levels, systolic blood pressure and HbA1c levels and taken from published sources. However, the explicit modelled link between weight loss data and clinical outcome measures has generally been poorly described. There is also little evidence to determine whether model inputs were always based on sex-specific data. Whilst it is clear that the goal of interventions modelled in the studies was to induce weight loss, and results were reported for men, the methods of extrapolating weight loss to long term sex specific outcomes are not always clearly presented. Indeed, weight loss data were poorly reported generally, with even less data presented on differences in weight loss by sex.

Some studies used Framingham risk equations [31] [33] to determine relative risks of cardiovascular events which were then linked, using a combination of literature and modelling exercises to final health outcomes and complications (e.g. diabetes, stroke, myocardial infarction etc.). Again, this was completed to varying degrees of complexity and data were not always clearly reported for weight loss or gender specific model inputs. Studies which failed to clearly report model data inputs are very difficult to generalise across groups, and would be theoretically difficult to re-produce in practice.

Three studies were cost-utility analyses [20] [22] [25], reporting results as cost per QALY gained. Such studies may be of greatest value to decision makers as they combine quality and length of life in one single outcome. Whilst the mortality (length of life) component was always well described, the methods used to derive utility weights were less clear. This has important implications for the generalizability of the results, particularly in an international context. One study reported cost per an average effectiveness score developed by the authors to reflect the importance of different grades of weight loss and the risk of developing obesity related complications [26]. The remaining three were cost-effectiveness analyses, reporting cost per life year gained [21] [23] [24].

Assumptions regarding the duration and continuation of treatment effect, for example weight loss and weight regain over time or changes in clinical risk factors (such as blood pressure) are crucial drivers of cost-effectiveness of weight loss interventions. Galani and colleagues assumed that weight loss was maintained over six years, with linear regain over four [20]. Therefore, after 10 years, it was assumed weight had returned to baseline levels. This assumption was validated against the Finnish Diabetes Prevention Study [29], however alternative assumptions were not explored in sensitivity analysis. While mortality and cardiovascular risk factors are based on sex-specific data and these are extrapolated to final outcomes, it is not clear if these were applied to sex-specific weight loss data or not. Maetzel and colleaguesassumed that patients receiving Orlistat would have weight loss over one year of therapy after which weight regain would be linear over three years, up to a point where weight would match that of the placebo group [24]. This assumption was tested in the author’s sensitivity analysis and was found to have an important impact on cost-effectiveness results. The remaining studies did not adequately document their assumptions about continuation of treatment effect over time. While such information is likely to be uncertain, it is important that the impact of any assumptions is thoroughly tested in sensitivity analyses.

All but one [26] of the studies attempted some form of sensitivity analysis, mainly focussing on issues of parameter uncertainty. Heterogeneity in study results was well accounted for across studies, with four out of five studies reporting results for key subgroups (e.g. impaired glucose tolerance (IGT), age groups, sex). All studies reported cost-effectiveness results for men and women separately, the only exception being Maetzel and colleagues [24], for which the base case model results were specific to men. Subgroup analyses conducted were appropriate to the study question and were generally clearly reported and interpreted. Where multi-variable sensitivity analyses were conducted, results were not always reported separately for men and women. Three studies [20] [22] [24] conducted extensive probabilistic sensitivity analysis, with uncertainty in cost-effectiveness estimates reported as cost-effectiveness acceptability curves (CEACs) and scatter plots. Again, however, illustrations were only reported for sex-specific subgroups in one study [20]. Comprehensive conduct of sensitivity analysis is crucial to determine the strength of a study's conclusions as well as the degree to which the results are generalizable to other setting, populations or countries.

A summary of the quality assessment for each study is provided in Table 3. More detailed comments on quality assessment forms for individual studies are available from the authors on request.

DISCUSSION

To our knowledge, this is the only systematic review of studies which evaluate the cost-effectiveness of interventions for the treatment of obesity in men. Although the studies retrieved offered some insights into the potential differences in cost-effectiveness of treatments for men and women, especially in relation to Orlistat, none of the studies specifically set out to determine sex specific cost-effectiveness results. As a result, it is not always clear that model inputs were sex-specific. Further, as it was not an original objective, no studies conducted the full range of sensitivity analyses on men and women separately. It was therefore not possible to assess the full range of uncertainty in reported cost-effectiveness estimates for men and women separately.

Our review does however provide some insights that these obesity treatments may offer good value for money. This was particularly evident in studies which targeted the highest risk groups in society, such as those with impaired glucose tolerance. Targeting these high risk groups could improve the cost-effectiveness case of treatments further. However, there was insufficient evidence reported to determine whether targeting at risk men had different cost-effectiveness outcomes from targeting at risk women.

Our review compliments a body of literature summarising the evidence on effectiveness and cost-effectiveness of obesity interventions. Lehnert and colleagues [11] provide a review of the cost-effectiveness literature, including studies which didn't report results separately for men and women. They found, similarly to our review, that the majority of interventions were cost-effective, or cost-saving. This complements the results of the studies included in our review. However caution should be noted when interpreting the broad suggestion of cost-effectiveness, as whether or not an intervention is cost-effective will be determined by the comparison which is made and the modelling for long-term weight loss maintenance. Lehnert specifically found that modifications to a target population's environment through fiscal and regulatory measures were the most cost-effective [11]. We found insufficient evidence to confirm this conclusion in men only studies. However, this is an area which warrants future research in men. Similarly to our review, Lehnert also found large uncertainty in reported cost-effectiveness results. This renders it difficult to draw firm conclusions. Further, study heterogeneity of interventions, comparators, modelling techniques, disease states considered and time horizon of costs and outcomes further complicate judgements about the comparative cost-effectiveness of interventions.

Our review concluded that there was a paucity of literature on the cost-effectiveness of non-surgical interventions to manage obesity in men. A recently published study reporting clinical outcome results, suggests that a community delivered intervention targeted at obese and overweight men in 13 Scottish professional football clubs offers promising results. The Football Fans In Training (FFIT) intervention [35] may also be a cost-effective use of resources, based on a preliminary economic evaluation presented in the trial results. However, in order to definitively determine cost-effectiveness we await the publication of results from the long term modelling exercise linked to this study.

Our review was conducted to address the cost-effectiveness of lifestyle and drug interventions to treat obesity in men. Nonetheless, surgery represents an important part in the obesity treatment pathway and is worthy of discussion. There are clear differences in the provision of bariatric surgery depending on sex. For example, in England in 2009 / 2010 obesity surgery was more common among women (5047 procedures) than men (1473 procedures) [36]. Obesity surgery has been found to be clinically and cost-effective [37, 38] and may even generate long term cost savings to health services providers in terms of reduced hospital contacts over a longer period of time [39]. Although there is good evidence on cost-effectiveness of bariatric surgery in the most obese population groups, the authors are unaware of any strong evidence relating to sex-specific cost-effectiveness. Determining whether or not there is a sex-specific element to the cost-effectiveness of obesity surgery, and if so what the drivers of this difference may be, are important avenues for future research. Robust evidence is required to determine if the current imbalance in provision of surgery by sex in the UK is a cost-effective use of scarce health services resources.

Whilst the studies included in our review point towards the cost-effectiveness of weight loss interventions, they should however be interpreted with caution and in light of their methodological limitations. Studies included were not explicitly designed to evaluate cost-effectiveness in men alone and it was thus not possible to fully evaluate the applicability of reported results to men only subgroups. For example, it was not always clear if data inputs were sex-specific and it was uncommon for uncertainty in men only analyses to be reported in detail. This renders it difficult to draw strong conclusions or provide guidance to policy makers interested in sex specific policy questions.

In terms of guidance for future good practice economic evaluation research, our review noted many strong and important assumptions regarding modelling of the continuation of treatment effect and weight loss maintenance over time across the studies, with no clear consensus on how this has been incorporated into the respective economic models. Studies which assume maintenance of incremental weight loss over time for the experimental group are likely to bias the analysis greatly in favour of the experimental intervention. Studies which conducted sensitivity analysis on assumptions around continuation of treatment effect over time, showed substantial variation in the presented ICERs. There is a clear lack of evidence on continuation of treatment effect to inform the models, however it is important that adequate sensitivity analyses are presented in order to fully inform decision makers regarding uncertainty in this important model parameter. Maintenance of treatment effect is likely to be determined mainly through adherence to lifestyle changes introduced at early stages of an intervention. Adherence to health lifestyle is an important driver of cost-effectiveness and one which has received insufficient coverage in the literature in general. Reviews of clinical effectiveness and qualitative literature conducted in parallel to this review address alternative measures which can motivate men and encourage adherence to interventions [13]. Engaging participants with interventions being tested and ensuring adherence to the therapy under evaluation is a key component of determining an interventions effectiveness, and hence its cost-effectiveness. Failure to engage participants in weight loss interventions can have a substantial impact on healthcare resource use, especially when rolled out to a large population of overweight or obese individuals. The impact on cost-effectiveness can be substantial, yet only one study in our review addressed the issue of adherence [25], finding that results were sensitive to the percentage of participants who fully adhered to the weight loss programme.

The framework of the analysis is a further important point to consider in economic evaluation. Cost-Utility analyses, reporting cost per QALY tend to be the gold standard for economic evaluation. The advantage of using QALYs is that they can improve the comparability of studies, and can thus be used to aid policy makers regarding resource allocation decisions. While QALYs are commonly used for this purpose, and are recommended by NICE, they only capture the health benefits of an intervention. There is scope for future research to consider broader measures of value, perhaps in the form of cost benefit analyses, which capture and include benefits associated with care processes and non-health outcomes. The inclusion of broader, preference based measures of outcome, such as discrete choice experiments (DCEs), can help to generate information on what is important to patients, and what they value most. DCEs can be used to determine the attributes of the processes and outcomes of care that are important to individuals, thus helping to improve adherence and weight loss maintenance. They can also be used in a cost-benefit analysis framework.

There is an urgent need for high quality economic evaluations, addressing a research question on cost-effectiveness of obesity related interventions for men. The long term economic results from the FFIT study [35] will undoubtedly be an important contribution to this literature. However, the target group is limited to football fans. Further high quality studies are required to assess the value for money of other targeted weight loss interventions for men. Such studies should systematically consider the available evidence on acceptability, effectiveness and costs associated with alternative interventions. Future research studies should be based on decision analytical models, with sex-specific model input data. Further consideration should be given to the methods used to link the effect of weight loss to overall disease risk. Some of our included studies seemed to suggest that small and even transient weight loss may have an impact on future disease risk and therefore could have an important impact on long-term effectiveness and cost-effectiveness outcomes. Maintenance of weight loss over time is an important parameter for cost-effectiveness and should be comprehensively tested in sensitivity analyses, with appropriate ranges of cost-effectiveness presented to decision makers. In this regard, studies should explicitly consider preferences of individual groups of the population to develop targeted ways in which to improve adherence and encourage long term maintenance of weight loss. This too will have important consequences for cost-effectiveness outcomes.

CONCLUSION

Our review did not identify any studies which evaluated the long term cost-effectiveness of weight loss interventions designed explicitly for men. However, the long-term economic results from the FFIT study [35] will help to begin to bridge a gap in this literature. There is some evidence that lifestyle interventions combining low fat (usually reducing), dietary advice and physical activity are likely to be cost-effective, and that Orlistat may be cost-effective in addition to a lifestyle intervention, especially when targeted at those with or at greatest risk of developing type 2 diabetes (e.g. those with IGT). However, there were no clear or systematic differences in cost-effectiveness of any of the interventions between men and women. There was insufficient evidence to draw strong conclusions on cost-effectiveness of weight loss interventions in men. Future studies should develop interventions which specifically target men. Economic evaluations should ensure that analyses are modelled over a sufficiently long time horizon to capture the most important costs and health outcomes attributable to weight loss interventions. Researchers are recommended to follow best practice guidelines for the conduct of economic evaluations alongside randomized controlled trials [40] and modelling studies [18]. Following specific best practice guidelines will improve the evidence base on cost-effectiveness and ensure the best quality economic evidence is provided to policy makers targeting weight loss in men.

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Table 1 **Summary of interventions evaluated in the retrieved economics studies**

Study	Country	Population group evaluated	Sex breakdown	Study Setting	Description of Intervention	Description of control / comparison
Galani 2007 [20]	Switz.	Overweight or obese adults (by Swiss standards), over the age of 25 with baseline BMI score of $\geq$27kg/m^2 (overweight) or BMI score of $\geq$ 33 kg/m^2 (obese)	Results reported for men and women together and for subgroups separately.	Primary care	Lifestyle intervention, consisting of: (i) Healthy Lifestyle advice (adapted on the Finnish Diabetes Prevention study [29] to include regular physical activity (participants recommended to undertake moderate intensity exercise for at least 30 minutes per day. Participants were also given detailed dietary advice, namely to (a) limit intake of fat to < 30% of energy consumed and of saturated fat to < 10%; (b) to increase fibre to at least 15g/1,000Kcal and (c) providing advice about specific food types. (ii) Ongoing support / counselling / consultations consisting of (a) Regular individual consultations with a dietician (7 visits to dietician in first year, 4 visits / year in years 2 and 3); (b) regular one hour long group based exercise sessions (n = 20 people), 4 classes / month in year 1; 2 classes / month in years 2 and 3.	There was no intervention given to overweight subjects. Obese subjects received less intense treatment, compared to the intervention group. Participants received basic dietary counseling (3 individual visits to the dietician in year 1, and once per year for years 2 and 3) and group based exercise sessions (20 people, one hour long sessions), twice per month in year 1 and once per year in years 2 and 3.
Ianazzo 2008 [22]	Italy	Population based on the XENDOS study [30] data and the Italian obese population, with a BMI$\geq$30; Italian obese population, ages 30-60, base case model age 35.	47.7% men; 52.3% women Model inputs were sex-specific	NR but assumed to be primary care.	4 years of treatment with Orlistat, 120mg three times per day in combination with low fat reducing diet and physical activity advice.	4 years placebo treatment, 3 times daily plus the same low fat reducing diet and physical activity advice.
Maetzel 2003 [24]	USA	Overweight and obese adults with type 2 diabetes	NR, model refers to age 52 men (UKPDS [31] study)	Assumed secondary care.	Treatment over an 11 year time horizon: Year 1: Orlistat + adherence to guideline therapy (ATG)** Years 2-11: ATG** only	Treatment over an 11 year time horizon with adherence to guidelines** only.

Study	Country	Population group evaluated	Sex breakdown	Study Setting	Description of Intervention	Description of control / comparison
Olsen 2005 [23]	Denmark	Obese patients with at least one of the following: BMI≥30kg/m^2 waist circ. > 102cm (men) and >88cm (women), Dyslipidaemia Type 2 diabetes.	NR, but results were presented based on sex-specific cardiovascular risk parameters.	Primary care (GP / Dietician clinics)	GP nutritional counselling: general lifestyle and healthy diet advice, (content unspecified). Intervention consisted of 6 counselling sessions over 12 months (1x30 mins. + 5x12 mins.). Patients provided with commercially available information on healthy diet. Dietician nutritional counselling: Provision of detailed advice on the principals of good nutrition (restricted total dietary energy, reduced fat, and cholesterol lowering diet. 6 consultations over 12 months (1x 60 mins. + 5 x 30 mins.).	Standard care – no active intervention.
Segal 1998 [21]	Australia	Persons with impaired glucose tolerance, overweight / obese men, seriously obese persons, women with previous gestational diabetes, general Australian population	Men only*	Primary care.	Group behavioural modification for men (5-6 group sessions, aim was to reduce waist size through diet change and increased activity, empowerment philosophy). Detailed information on intervention content was not available.	Standard care – no active intervention.
Miners, 2012 [25]	UK	Obese adults with a BMI≥30kg/m^2 Base case model for average 50 year old male	Results reported by sex sub-group. Most other analyses on men only	Primary care	An E-learning device, based on that reported in McConnon et al, 2007 [32], used to provide advice, tools and information to support behavior change in dietary and exercise patterns. Based on patient self-management and individualized based on their own needs. Advice was personalized and given in response to a series of online questions. Motivational statements and emails automatically	A generic, non-specified conventional care package, including dietary and exercise information. A crude comparison vs. Orlistat was also modelled, though not formally presented. Purpose was contextual only.

					provided, especially to those not visiting the site often. 12 months subscription to site.	
Study	**Country**	**Population group evaluated**	**Sex breakdown**	**Study Setting**	**Description of Intervention**	**Description of control / comparison**
Spyra, 2014 [26]	Germany	55 year old male with a BMI≥30kg/m^2 who has already developed Type II Diabetes	Results applicable to a 55 year old male	Not clear – assume primary care / comm. programme.	4 interventions: A) Body-Med nutrition concept: 2 phase programme, phase 1 included the use of protein rich meal replacements. Phase 2 focused on maintenance with medically controlled long term care (details not provided). Other components included behavioural therapy and exercise. Programme carried out by specially trained professionals. Frequency of delivery / contact not reported. B) MOBILIS Programme: an interdisciplinary training programme centered on exercise, psychology, nutrition and medicine. Details on content not reported. Programme duration: 1 year; Frequency of contact not reported. Provided by specially trained medical and non-medical professionals. C) DGE ('I am Losing Programme'): High carbohydrate, low fat diet (no solid food plans), 3 month programme can be carried out in structured groups or on one's own. Participants follow a 12 step manual to a healthy diet. Physical exercise is also incorporated. D) Therapeutic Nihilism: No medically attended or structured programme but tries to lose weight on their own. Patients provided with basic guidance on healthy eating, diet and exercise only. Not medically or professionally supervised in any way.	None reported, though it could be assumed that the therapeutic Nihilism could be considered a baseline comparator. However, results are not presented in this way.

*A total of five alternative programmes were evaluated in the study, however as only programme IV presented results specific to men, the others have not been included.

** ATG = adherence to guidelines; standard pharmacotherapy for type 2 diabetes (e.g. metformin) and weight management (diet and physical activity)

ATG = Adherence to Guidelines; BMI = Body Mass Index; DGE: Deutsche Gesellschaft für Ernählung (translated from German as the German Society for Nutrition); GP = General Practitioner; Mg. = Milligrams; Mins = Minutes; MOBILIS: Multizentrisch Organisierte Bewegungsorientierte Initiative zur Lebensstiländerung In Selbstverantwortung (translated from German as a Multi-centre movement oriented initiative for lifestyle change through self-

responsibility); NR = Not Reported; UKPDS = United Kingdom Prevention of Diabetes Study; XENDOS = XENical for the preventions of Diabetes in Obese Subjects.

Table 2 Detailed cost and outcome data from the studies[A]

Study	Int.	Comp.	Model Time Horizon	Currency (year)	Base case discount rates	Primary economic outcome measure	Inc. costs, Study currency (2014 GBP)[F]	Inc. Outcomes [F]	ICER; study currency (2014 GBP) [F]	ICER range from sensitivity analyses study currency (2014 GBP) [F]	Results from probabilistic sensitivity analysis (if applicable)
Galani 2007 [20]	Lifestyle	O/W group (std. care); obese group (lifestyle advice)	60 years or to max age of 85.	Swiss francs (CHF), (2006).	Costs – 3% Effects – 3%	QALY	O/W: +405(+£204) B/L: -6(-£3) OB:+127 (+£64)	O/W: +0.25 B/L: +0.28 OB: +0.29	NR for all age groups, calc as: O/W: 1,620 (£816) B/L: Dominant OB: 438 (£220)[C]	Dominant to +2,014 (£1,014)	Data only presented for B/L obesity. 57% probability of cost-effectiveness (35 year old male) to 72% probability (55 year old male) at a willingness to pay of 0 CHF per QALY gained. 92% probability of cost-effectiveness (35 year old male) to 98% probability (55 year old male) at a willingness to pay of 1000 CHF per QALY gained.
Ianazzo 2008 [22]	Orlistat + lifestyle	Placebo+ lifestyle	10 years	Euro, (2007)[B]	Costs – 3.5% Effects – 3.5%	QALY	+2,931 (£2,850)	+0.046	74,290 (£72,249)	M only: NR M+W: 10,160 (£9,881) to 79110 (£76,937)	Men only: NR. Men and Women: 15% probability of cost-effectiveness at a willingness to pay of €45,000 per QALY gained (base case analysis), increasing to 99% probability for a subgroup with IGT.
Maetzel 2003 [24]	Orlistat + standard treatment guidelines	Standard treatment guidelines alone.	11 years	USD (2001)	Costs – 3% Effects – 3%	Event free life years gained	+1,099 (£1,008)	+0.162	+8,327 (£7,553)	+8,327 (£7,553) to +25,827 (£23,426)	95% probability of cost-effectiveness at a willingness to pay of $20,000 (i.e. £18,140) per event free life year gained, assuming continuation of treatment effect over 3 years. 95% probability of cost-effectiveness at a willingness to pay of $68,000 (£61,674) per event free life year gained, assuming continuation of treatment effect for 1 year only.”

Study	Int.	Comp.	Model Time Horizon	Currency (year)	Base case discount rates	Primary economic outcome measure	Inc. costs, Study currency (2014 GBP)[F]	Inc. Outcomes [F]	ICER; study currency (2014 GBP) [F]	ICER range from sensitivity analyses study currency (2014 GBP) [F]	Results from probabilistic sensitivity analysis (if applicable)
Olsen 2005 [23]	GP or dietician counselling	Standard care	Costs – 1 year Effects – up to age 80.	Danish Kroner (2001)	Costs – none Effects – 5%	Life years gained	Diet: 1,684 (£190) GP: 774 (£87)	Diet: 0.0002 GP: 0.1210	Diet: NR, calc as 8.42m (£949,227) GP: 6,399 (£640)	Diet: 26,730 (£3,013) to 6.155m (£687,682) GP: 3,240 (£365) to 24,037 (£2,710)	N/A
Segal 1998 [21][D]	Group behavior modification	Standard care	25 years post intervention	Australian Dollars (1997)	Costs – 5% Effects – 5%	Life years gained	Prog IV Intervention cost = 577 (£380) Total cost: NR	Prog IV Mixed[D] GT: +111[E] IGT: +138[E]	Prog IV (net costs) Mixed[D] GT: Dominant IGT: Dominant	Prog IV Dominant to 1,600 (£1,054)	N/A
Miners, 2012 [25]	E- learning device	Standard care (conventional care package)	Life time	GBP (2009)	Costs – 3.5% Effects – 3.5%	QALY	+£762 (+£880)	+0.007	£102,112 (£117,963)	Dominant to £232,911 (£269,067)	<50% probability of the E-learning device being cost effective up to a WTP of £200,000 / QALY gained.
Spyra, 2014 [26]	A) Bodymed – nutrition B) MOBILIS C) DGE ('I am losing') D) Nihilism	None stated (Assume no care)	3 years	EUR (2012)	Costs – 3% Effects – NR	De novo effect score (based on weight and clinical events)	A) 3,595 (£2,997) B) 4,248 (£3,541) C) 3,704 (£3,088) D) 3,696 (£3,081)	A) 3.75 B) 2.55 C) 1.90 D) 1.17	A) 957 (£798) B) 1,669 (£1,391) C) 1,948 (£1,624) D) 3,172 (£2,644)	NR	NR

[A]Results are for men only, unless otherwise stated; [B]Year 2007 costing assumed based on reference lists for unit costs; [C]Based on author calculations from included studies; [D]Programme IV results for men only, presumed a mix of normal glucose tolerance, impaired glucose tolerance and type 2 diabetes; [E]Cohort size of 100 patients; [F] ICERs may not always = incremental costs / incremental outcomes in the table above. This is due to the potential for rounding errors in

calculations. Data reported for ICERs are as reported in the studies. B/L = Borderline; CHF= Swiss Francs; DGE: Deutsche Gesellschaft für Ernählung (translated from German as the German Society for Nutrition); GBP = Great British Pounds; GP = General Practitioner; ICER = Incremental cost-effectiveness ratio; IGT= Impaired Glucose Tolerance; Inc. = Incremental; M= Men; MOBILIS: Multizentrisch Organisierte Bewegungsorientierte Initiative zur Lebensstiländerung In Selbstverantwortung (translated from German as a Multi-centre movement oriented initiative for lifestyle change through self-responsibility); N/A = Not applicable; NR = Not Reported; OB = Obese; O/W = overweight; QALY = Quality Adjusted Life Year; USD = US dollars; W = Women; WTP = Willingness to Pay

Supplementary Table 3: Quality assessment of studies (based on Phillips checklist [18])

Study name and year:			**Galani 2007** [20]	**Ianazzo 2008** [22]	**Maetzel 2003** [24]	**Olsen 2005** [23]	**Segal 1998** [21]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
Structure:									
S1	Statement of decision problem / objective	Clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y
		Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y
		Is the primary decision maker specified?	N	N	N	N	N	Y	Y
S2	Statement of scope / perspective	Is the perspective of the model clearly stated?	Y	Y	Y	?	Y	Y	Y
		Are the model inputs consistent with the stated perspective?	N	N	Y	N	Y	Y	Y
		Has the scope of the model been stated and justified?	Y	Y	N	N	Y	Y	Y
		Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	?	?	Y	Y
S3	Rationale for structure	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	N	Y	Y	Y
		Are the sources of data used to develop the structure of the model specified?	Y	Y	N	N	N	Y	N

		Are the causal relationships described by the model structure justified appropriately?	Y	Y	Y	Y	N	Y	Y
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
S4	Structural assumptions	Are the structural assumptions transparent and justified?	Y	Y	Y	?	Y	Y	N
		Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	N	Y	Y	Y
S5	Strategies / Comparators	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	?	Y	Y
		Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y	Y
		Is there justification for the exclusion of feasible options?	N/A	N/A	N/A	N/A	Y	N/A	N/A
S6	Model type	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	Y	Y	N	Y	Y	Y
S7	Time horizon	Is the time horizon of the model sufficient to reflect all important differences between options?	Y	?	?	N	Y	Y	N
			Y	Y	Y	Y/N	?	Y	N

		Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?							
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
S8	Disease states / pathways	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	N/A	Y	Y	Y
S9	Cycle length	Is the cycle length defined and justified in terms of the natural history of disease?	Y	Y	Y/N	N/A	Y/N	NA	Y/N
Data:									
D1	Data identification	Are the data identification methods transparent and appropriate given the objectives of the model?	Y/N	Y/N	Y	Y	?	Y	Y
		Where choices have been made between data sources, are these justified appropriately?	N	?	N	?	?	Y	N
		Has particular attention been paid to identifying data for the important parameters in the model?	Y	Y/N	Y	Y	Y	Y	?

		Has the quality of the data been assessed appropriately?	Y	Y	?	N	N	N	N
		Where expert opinion has been used, are the methods described and justified?	N/A	N/A	N/A	N/A	N	NA	NA
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
D2	Data modelling	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	Y	Y	Y	Y	Y	Y
D2a	Baseline data	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y/N	Y	Y
		Are transition probabilities calculated appropriately?	?	Y	?	N/A	?	NA	Y
		Has a half cycle correction been applied to both cost and outcomes?	N/Y	N	N	N/A	N	NA	?
		If not, has this omission been justified?	N/A	N	N	N/A	N	NA	N
D2b	Treatment effects	If relative treatment effects have been derived from the trial data, have they been synthesized using appropriate techniques?	Y	Y	?	?	?	Y	?

		Have the methods and assumptions used to extrapolate short term results to final outcomes been documented and justified?	Y	Y	Y	Y	Y	Y	Y
		Have alternative extrapolation assumptions been explored through sensitivity analysis?	N	N	Y	N	N	Y	N
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
		Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	Y	Y	Y/N	Y	Y	Y
		Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N	N	Y	N	Y	Y	N
D2c	Costs	Are the costs incorporated into the model justified?	Y	Y	Y	N	Y	Y	Y
		Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	Y
		Have discount rates been described and justified given the target decision-maker?	Y	Y	Y	Y	Y	Y	Y
D2d	Quality of life weights (utilities)	Are the utilities incorporated into the model appropriate?	?	Y	N/A	N/A	N/A	Y	N/A

		Is the source for the utility weights referenced?	Y	Y	N/A	N/A	N/A	Y	N/A
		Are the methods of derivation for the utility weights justified?	?	?	N/A	N/A	N/A	N	N/A
D3	Data incorporation	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	Y	Y	Y	Y/N	Y	N
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
		Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	N/A	N/A	N/A	N/A	N/A	Y	N/A
		Is the process of data incorporation transparent?	Y	Y	Y	Y	N	Y	Y
		If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Y	Y	N/A	N/A	N/A	?	N/A
		If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Y	Y	Y	N/A	N/A	Y	N/A
D4	Assessment of uncertainty	Have the four principal types of uncertainty been addressed?	N	N	N	N	N	N	N
		If not, has the omission of particular forms of uncertainty been justified?	N	N	Y	N	N	N	N

D4a	Methodological	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	Y	Y	Y	N	Y	N
D4b	Structural	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	Y	N	Y	N	N
D4c	Heterogeneity	Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	Y	N	Y	Y	Y	N
Study name and year:			**Galani 2007** [19]	**Ianazzo 2008** [21]	**Maetzel 2003** [23]	**Olsen 2005** [22]	**Segal 1998** [20]	**Miners 2012** [25]	**Spyra 2014** [26]
Quality Criterion	**Dimension of Quality**	**Question**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**	**Response Y/N/NA/?**
D4d	Parameter	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	?	Y	N
		If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	Y	Y	N/A	Y	Y	N
Consistency:									
C1	Internal consistency	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	Y	N	N	N	N	N
C2	External consistency	Are any counterintuitive results from the model explained and justified?	Y	N/A	N/A	N/A	N/A	Y	N
		If the model has been calibrated against independent data, have	Y	Y	N	N/A	N	Y	N

		any differences been explained and justified?							
		Have the results of the model been compared with those of previous models and any differences in results explained?	Y	Y	Y	Y	N	Y	N

Appendix 1: Cost-effectiveness search strategies – MEDLINE and Embase

MEDLINE (1946 to 24 October 2014);

MEDLINE In-Process & Other Non-Indexed Citations (24 October 2014);

EMBASE (1974 to October 2014)

Ovid multifile search: http://shibboleth.ovid.com/

1. exp “costs and cost analysis”/
2. cost-benefit analysis/
3. quality-adjusted life years/
4. economics,pharmaceutical/
5. exp budgets/
6. exp models, economic/
7. exp decision theory/
8. monte carlo method/
9. markov chains/
10. exp health status indicators/
11. cost$.ti.
12. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
13. economic$ model$.tw.
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw.
15. (price$ or pricing).tw.
16. (financial or finance or finances or financed).tw.
17. ((value adj2 money) or monetary).tw.
18. markov$.tw.
19. monte carlo.tw.
20. (decision$ adj2 (tree? or analy$ or model$)).tw.

21. (standard adj1 gamble).tw.

22. trade off.tw.

23. or/1–22

24. *obesity/

25. *overweight/

26. obesity, morbid/ use prmz

27. morbid obesity/ use oemez

28. (obes$ or overweight).tw.

29. weight loss/ use prmz

30. weight reduction/ use oemez

31. (weight adj1 (los$ or reduc$ or maint$ or control or manag$)).tw.

32. (obesity adj1 management).tw.

33. (anti obesity or antiobesity).tw.

34. or/24–32

35. (men or male or males).tw.

36. *obesity/ec

37. *overweight/ec

38. or/36-37

39. (women not men).tw.

40. (female not male).tw.

41. 38 not (39 or 40)

42. 23 and 34 and 35

43. 41 or 42

44. exp animals/ not humans/

45. 43 not 44

46. (rat or rats).tw.

47. 45 not 46

48. limit 47 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "all adult (19 plus years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

49. limit 47 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years>or adolescent <13 to 17 years>)

50. 47 not 48

51. 47 not 49

52. 50 or 51

53. limit 52 to yr="2009 -Current"

54. remove duplicates from 53

55. (letter or editorial or comment or note).pt.

56. 54 not 55