Accepted refereed manuscript of:

Boyers D, Avenell A, Stewart F, Robertson C, Archibald D, Douglas F, Hoddinott P & van Teijlingen E (2015) A systematic review of the cost-effectiveness of non-surgical obesity interventions in men, *Obesity Research and Clinical Practice*, 9 (4), pp. 310-327.

1   **A SYSTEMATIC REVIEW OF THE COST-EFFECTIVENESS OF NON-SURGICAL**

2   **OBESITY INTERVENTIONS IN MEN**

3

4   Dwayne Boyers[1,2] M Econ. Sc.

5   Alison Avenell[1] MD FRCP

6   Fiona Stewart[1] MSc

7   Clare Robertson[1] MSc

8   Daryll Archibald[2,3] PhD

9   Flora Douglas[4] PhD RN

10   Pat Hoddinott[5] PhD FRCGP

11   Edwin van Teijlingen[6] PhD

12

13   1. Health Services Research Unit, University of Aberdeen, Health Sciences Building, Foresterhill,

14   Aberdeen, AB25 2ZD

15   2. Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill,

16   Aberdeen, AB25 2ZD

17   3. Centre for Academic Primary Care, University of Aberdeen, Drew Kay Wing, Foresterhill,

18   Aberdeen, AB25 2ZD

19   4. Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road,

20   Aberdeen, AB21 9SB

21   5. Nursing, Midwifery and Allied Health Professional Research Unit, University of Stirling, Stirling, FK9 4LA

22   6. Centre for Midwifery, Maternal & Perinatal Health, Bournemouth University,

23   Bournemouth House B112, 19 Christchurch Road, Bournemouth, Bournemouth BU1 3LH.

24

25

26

27

28 **Corresponding author:**

29 Dwayne Boyers

30 Health Services Research Unit / Health Economics Research Unit

31 University of Aberdeen

32 3rd Floor, Health Sciences Building

33 Foresterhill

34 Aberdeen AB25 2ZD

35 d.boyers@abdn.ac.uk; Tel: 0044 (0) 1224437850; Fax: 0044 (0) 1224437195

36

38

39 **Running Title:** Cost-effective treatments for obese men

40

52

53 **Conflicts of Interest:**   None

54 **Abbreviations**

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

82   CHF: Swiss Francs

83   GBP: Great British Pounds

84   FFIT: Football Fans In Training

85   UKPDS: United Kingdom Prevention of Diabetes Study

86

87 **Abstract:**

88 **Background:**

89 Increasing obesity related health conditions have a substantial burden on population health and

90 healthcare spending. Obesity may have a sex-specific impact on disease development, men and women

91 may respond differently to interventions, and there may be sex-specific differences to the cost-

92 effectiveness of interventions to address obesity. There is no clear indication of cost-effective

93 treatments for men.

94

95 **Methods:**

96 This systematic review summarises the literature reporting the cost-effectiveness of non-surgical

97 weight-management interventions for men. Studies were quality assessed against a checklist for

98 appraising decision modelling studies.

99

100 **Results:**

101 Although none of the included studies explicitly set out to determine the cost-effectiveness of treatment

102 for men, seven studies reported results for subgroups of men. Interventions were grouped into lifestyle

103 interventions (five studies) and Orlistat (two studies). The retrieved studies showed promising evidence

104 of cost-effectiveness, especially when interventions were targeted at high-risk groups, such as those

105 with impaired glucose tolerance. There appears to be some sex-specific elements to cost-effectiveness,

106 however, there were no clear trends or indications of what may be contributing to this.

107

108 **Conclusion:**

109 The economic evidence was highly uncertain, and limited by variable methodological quality of the

110 included studies. It was therefore not possible to draw strong conclusions on cost-effectiveness. Future

111 studies are required to demonstrate the cost-effectiveness of interventions specifically targeted towards

112 weight loss for men.

113

114 **INTRODUCTION:**

115

Overweight and obesity are significant population health concerns. US data from 2007-2010 show that based on having a BMI (Body Mass Index) $\geq 30\text{kg/m}^2$, 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 $\geq 40\text{kg/m}^2$) 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.

127

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 $\geq 30\text{kg/m}^2$ and waist circumference $\geq 102\text{cm}$ 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 $< 30\text{kg/m}^2$ [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].

140

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

143   BMI for every adult, based on baseline values could save 3,195,000 QALYs by 2030 [8]. Despite some

144   uncertainty in the literature regarding the assumptions underpinning the future trends in obesity

145   worldwide [9] [10], there is general consensus that obesity rates will continue to increase into the near

146   future, with significant impact, not only on health care costs, but also on population health, quality of

147   life and the social, economic and emotional costs to those individuals affected.

148

149   The burden of obesity on healthcare and wider economic costs has motivated the evaluation of clinical

150   effectiveness and cost-effectiveness of a range of treatment strategies, including drug therapy, surgery,

151   diet and physical activity, all of which have been shown to have varying degrees of success, regardless

152   of sex, in modifying the obesity problem. Recent systematic reviews have summarized the current

153   literature on the long term cost-effectiveness of obesity prevention interventions generally [11], and the

154   cost-effectiveness of therapeutic interventions [12].

155

156   This purpose of this article is to report an updated systematic review of the cost-effectiveness of non-

157   surgical treatments in the management of obesity in men and to summarize the literature on this

158   important topic. The original work formed part of a larger research project funded by the National

159   Institute for Health Research (NIHR) Health Technology Assessment (HTA) program [13], which

160   reviewed the clinical and cost-effectiveness and qualitative literature on obesity management for men,

161   since men are much less likely to take part in trials or evaluations of weight loss interventions [14].

162   This report [13] found clear evidence that policy makers should take account of sex and gender

163   differences when designing services for obesity management, and that design differences between men

164   and women may influence uptake, effectiveness, dropout rates and costs.

165   This article reports the costs, outcomes and cost-effectiveness of a range of strategies for the

166   management of obesity in adult men, with an appropriate quality assessment of the included studies,

167   based on best practice economic evaluation methodology.

168   **METHODS:**

169

**Identification of studies:**

172   An extensive and highly sensitive search strategy using appropriate subject headings and text word

173   terms was developed to identify alternative strategies for weight loss, with a distinct and interpretable

174   focus on strategies for the management of obesity in adult men [13]. The literature search included

175   both ongoing studies and grey literature. Databases searched were: MEDLINE (1946 –October 2014);

176   MEDLINE-in-Process (24th October 2014); Embase (1974 – October 2014); Health Management

177   Information Consortium (1979 – October 2014); National Health Service (NHS) Economic Evaluations

178   Database; Cost-effectiveness Analysis Registry; Research Papers in Economics (all searched up to

179   October 2014). No language restrictions were imposed, however the search was limited to studies

180   published post 1990. Full details of the search strategy used for the MEDLINE and Embase databases

181   are presented in Appendix 1 to the paper. Further details of the search strategies for other databases are

182   available from the authors on request.

183

184   _**Inclusion and exclusion criteria:**_

185

186   Economic evaluations, with full description of economic methods and results conducted alongside

187   randomized trials and _de novo_ decision analytical models that comparatively analyzed costs and

188   outcomes in an economic evaluation framework were included. Methodological papers, review papers,

189   cost of illness papers and studies which did not conduct a formal comparison of costs and outcomes

190   (i.e. those studies which did not conduct a full economic evaluation) were excluded. A full economic

191   evaluation was defined as a cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis or

192   cost-minimisation analysis framework. We excluded studies from this review which reported limited

193   cost-effectiveness outcomes, as the primary purpose of the publication was to present clinical results.

194   Such studies were excluded as they would not present methods and / or results in sufficient detail, and

195   we could not quality assess the study.

196

197 Studies were included if they reported results either wholly or for a sub-group of men (mean or median

198 age of 16 years or over, with no upper age limit). Studies particularly examining men with obesity

199 related to psychotropic medication, diagnosed eating disorder or with learning disabilities were

200 excluded. The following interventions were included: Orlistat (but not Sibutramine or Rimonabant,

201 which no longer have European Medicines Agency licenses); diet; physical activity; behaviour change

202 relating to weight loss; or combinations of any of these. Complementary therapies, surgical procedures

203 and other medications were excluded. Economic evaluation studies were only included if their main

204 aim was to evaluate the cost-effectiveness of weight loss interventions. Studies examining

205 combinations of interventions, other than the combinations outlined above, were not included. For

206 example, we did not include interventions combining smoking cessation with weight loss. Studies were

207 therefore deemed fit for inclusion in the review if they were full economic evaluations producing weight

208 loss, where results were reported solely or for sub-groups of men.

209

210 ***Study selection, data extraction and reporting***

211

212 Data extraction was undertaken by the project health economist (DB). Data extraction forms were

213 checked by a second member of the review team (AA) for consistency and accuracy. The data

214 extraction process focused on two key areas: (i) the results of the economic evaluations in terms of

215 estimates of costs and effects; and (ii) the methods used to derive the results. Summary data from each

216 study are reported and a narrative discussion is presented. The aim of the narrative is to identify

217 common results, methodological strengths and weaknesses across interventions and to inform future

218 applied and methodological research. Due to the wide variation in reported currencies and costing

219 years, we have inflated costs from the study year of reporting to 2014 values using appropriate inflation

220 indices for each individual country [15] [16], and converted to UK £, using purchasing parity indices

221 provided by the Organization for Economic Co-operation and Development (OECD) for non-UK

222 studies[17]. The presentation of data from the studies in common year and currency estimates is to

223 facilitate a discussion of the results across broad intervention groups, but is not intended in any way to

224   represent a formal quantitative synthesis of the data. All included studies were quality assessed using

225   the Philipp's checklist for decision modelling in economic evaluations [18].

226

227   ***Reporting of economic evaluations:***

228

229   Included studies report costs, outcomes and synthesize these estimates within a formal economic

230   evaluation framework. Economic evaluations are based on the principles of scarcity and choice. Many

231   healthcare interventions may improve patient outcomes. However, healthcare resources are scarce, and

232   so decision makers have to make choices on the best way to spend their limited health budgets.

233   Economic evaluation is a way in which we can attempt to allocate money to health care interventions

234   in the most efficient way possible, gaining maximum health outcome with restricted investment. There

235   are two main methods of economic evaluation which have been included in this review, namely cost-

236   effectiveness analyses (CEA) and cost-utility analyses (CUA). Both present a comparison of the

237   additional costs of a new intervention with the improvement in outcomes. Results are usually presented

238   in terms of the Incremental Cost-Effectiveness Ratio (ICER), which is simply given as [(Cost of new

239   intervention – Cost of standard) / (Outcomes of new intervention – outcomes of standard)]. Lower

240   values of the ICER are preferred as they offer better value for money. The difference between CEA

241   and CUA lies in how outcomes are measured. For CEA, outcomes are measured in terms of natural

242   units, such as life years gained, reduced cases of diabetes etc. For CUA, outcomes are typically

243   measured in terms of QALYs, which combine benefits in reduced mortality with a measure of quality

244   of life. QALYs are the preferred outcome measure for decision making bodies such as the National

245   Institute for Health & Care Excellence (NICE), the European Network for technology assessment

246   (EUnetHTA), the Canadian Agency for Drugs and Technology in Health (CADTH) and other decision

247   making bodies as they provide a common metric for the comparison of new interventions across the

248   health services. Each country and decision making body will have their own criteria for recommending

249   interventions as cost-effective. For example, NICE typically recommend interventions for

250   reimbursement in the UK if the cost of achieving a one unit improvement in QALYs is less than £30,000

251   ((i.e. an ICER < £30,000 per QALY) [19]. Further, if an intervention which improves QALYs is found

252   to also generate long term cost savings, for example if cost savings achieved from reducing long term

253   incidence of coronary heart disease were greater than the costs of intervening now, then this offers an

254   even stronger case for cost-effectiveness and is reported as being cost saving or the "dominant"

255   intervention in the analysis. As obesity is a predictor for the development of chronic health conditions,

256   we are interested not only in short term outcomes from randomized controlled trials (RCTs), but also

257   in the longer-term costs and outcomes associated with differential risks of developing chronic diseases

258   such as diabetes and heart disease. It is therefore common economic evaluation practice to extrapolate

259   short-term outcomes from clinical trials (e.g. blood pressure, cholesterol levels, BMI) to longer term

260   health outcomes, such as risk of disease and mortality as well as the healthcare costs associated with

261   such diseases over a patient's lifetime. In order to make these predictions, economic evaluations

262   typically use decision analytical models, often Markov models, which estimate future costs and

263   outcomes attributable to an intervention based on the probability of developing diseases into the future.

264   This extrapolation of costs and outcomes forms an important tool in economists' evaluation of

265   healthcare interventions.

266

267

268   **RESULTS:**

269

270   Original searches of the literature were conducted to 2012 and updated to 2014. In total, the primary

271   searches identified 2,333 potentially relevant titles and abstracts, 90 studies were selected for full text

272   retrieval to further assess their eligibility criteria for our study. Upon reading all full text papers, a total

273   of seven studies [20] [21] [22] [23] [24] [25] [26] were deemed to meet our inclusion criteria and were

274   formally included for the review and quality assessment. A flow chart of included studies from the

275   original review is available from the original project report [13]. Due to study heterogeneity, we did

276   not undertake formal meta-analysis of results. Therefore, a narrative discussion of the cost-

277   effectiveness results is presented with included studies grouped into two categories: 1) studies that focus

278   on lifestyle interventions (5 studies [20] [21] [23] [25] [26]) and 2) studies that focus on Orlistat

279   pharmacotherapy (2 studies [22] [24]). In addition to the included studies, we retrieved two further

280   clinical guideline documents [27] [28] from NICE, the first of which briefly discusses sex-specific

281   issues in the cost-effectiveness or Orlistat [27], with the latter guidance relating to the management of

282   overweight and obese adults through lifestyle weight management services [28]. Detailed study

283   characteristics, interventions and comparator treatments evaluated in the studies are presented in Table

284   1 whilst the main cost-effectiveness results are presented in Table 2.

285

286   *Lifestyle interventions:*

287

288   Segal and colleagues [21] found that a group diet and physical activity behavioural modification

289   intervention for men, was both cost saving to health services and also more effective than providing no

290   routine care, thus demonstrating favourable cost-effectiveness results. The intervention was most cost-

291   effective when restricted to those at greatest risk of type II diabetes (i.e. those with impaired glucose

292   tolerance). The study conclusions were robust to plausible variation in the treatment success rate of the

293   programme.

294

295   Olsen and colleagues [23] found that General Practitioner (GP) counselling was more cost-effective

296   than dietician provided counselling to encourage weight loss and reduce the risk of developing

297   ischaemic heart disease (IHD) or death. It should be noted however that there were important

298   differences in the content of the advice provided to the different groups. GP advice included general

299   broad lifestyle advice and the delivery of commercially available information on healthy diet, whereas

300   dietician provided advice was more focussed and concentrated on the principles of good nutrition.

301   The authors speculate that favourable results for GP consultations may be driven by the additional

302   general health advice which they routinely provided. Despite the cost-effectiveness results favouring

303   GP over dietician support, the authors conclude that the role of the dietician should not be discounted,

304   especially given health care provider constraints in practice.

305

306   Galani and colleagues [20] found that a structured lifestyle intervention (including regular dietician

307   visits and supervised exercise sessions), delivered to overweight and obese adults over the course of

308   three years was dominant (cost saving and more effective) for borderline obese and was also highly

309   cost-effective for overweight and obese men, with low ICERs, offering excellent value for money to

310   health services providers. Results were also robust to sensitivity analyses, adding to the strength of the

311   study's conclusions.

312

313   Miners and colleagues [25] evaluated an e-learning device with tailored feedback to participants over a

314   lifetime horizon using a discrete event simulation model, but did not find evidence to prove cost-

315   effectiveness compared to a conventional care package including dietary and physical exercise advice.

316   The results were highly sensitive to the cost of providing the online programme and the authors note

317   that their conclusions should not be generalized to all web-based interventions.

318   Spyra and colleagues [26] evaluated four alternative lifestyle interventions against a 'do nothing'

319   approach. Three commercially provided programs, involving specially trained providers, for German

320   social health insurance funds and therapeutic nihilism (with no medical or specialist intervention) were

321   compared. A two phase programme of protein rich meal replacement followed by a maintenance phase

322   with medically controlled long term specialist care was found to be the most cost-effective treatment

323 option. Specific intervention details were however not provided rendering it difficult to assess the

324 applicability or generalizability of the results.

325 *NICE Guidance on Lifestyle Interventions:*

326

327 NICE have also recently issued guidance on lifestyle weight management for overweight and obese

328 adults [28], which included a review of the literature on cost-effectiveness and additional sex specific

329 modelling of longer term costs and effects. The results of the review showed lifestyle interventions to

330 be cost-effective, but studies were of variable quality. The additional modelling carried out showed

331 that lifestyle interventions costing £100 per person for a 12 week programme, or costing £200 for a 24

332 week programme would be cost-effective if the amount of weight lost is maintained for life. Whilst

333 sex was found to be an influencing factor, it was not a major driver of cost-effectiveness results.

334 However, the model was highly sensitive to the assumptions surrounding maintenance of weight loss,

335 showing that if weight was regained over 2 years or less, such interventions would no longer be cost-

336 effective. The length of required weight loss maintenance required for cost-effectiveness was less for

337 older people. Maintenance of weight loss over time is a critical driver of cost-effectiveness, and further

338 research is required to identify the best evidence for populating economic models.

339

340 **Drug treatment with Orlistat:**

341

342 Two studies estimated the cost-effectiveness of Orlistat in overweight and obese men. Ianazzo and

343 colleagues [22] reported a cost-utility analysis of Orlistat (120mg, three times daily), over a four year

344 time period in addition to a lifestyle intervention (dietary and physical exercise components) for the

345 prevention of type 2 diabetes, in an Italian obese population. There was no clear evidence that Orlistat

346 was cost-effective in overweight and obese men. However, the results were highly sensitive to the level

347 of risk of developing diabetes. Therefore, the authors concluded that if the drug was targeted at a high

348 risk group, then the treatment was much more likely to be a cost-effective use of healthcare resources.

349

350   Maetzel and colleagues [24] evaluated Orlistat 120mg taken three times daily for only one year in

351   addition to standard treatment guidelines for type 2 diabetes (an 11 year diabetes treatment programme)

352   in a US healthcare setting. Standard diabetes care included pharmacotherapy (e.g. metformin) and

353   weight management in the form of dietary and physical activity advice. Orlistat was found to be cost-

354   effective. However, the authors note that conclusions were highly sensitive to the duration of treatment

355   effect, with greater duration of effect greatly improving cost-effectiveness. Observational data to

356   support long term use of Orlistat in this population are needed to validate the results of the study.

357

358   *National level Guidance on the use of Orlistat:*

359

360   Our review identified one clinical guideline document which evaluated the cost-effectiveness of

361   Orlistat, and presented data separately for men and women. The National Institute for health and Care

362   Excellence (NICE), the UK's decision making body for the recommendation of treatments for

363   reimbursement on the NHS, has issued obesity guidelines (clinical guideline number 43) [27], which

364   included an update of original NICE guidance on Orlistat (Technology Appraisal number 22) [34].

365   Additional modelling work was undertaken to estimate sex-specific quality of life weights to inform

366   QALY calculations, and for use in subsequent economic modelling exercises. Sensitivity analyses

367   reported QALY and cost per QALY outcomes separately for men, based on available effectiveness

368   (weight loss) and cost data for Orlistat. There was no evidence of differing cost-effectiveness for men

369   and women based on 12 months' treatment with Orlistat, with ICERs well below a commonly

370   acceptable willingness to pay of £20,000 per QALY gained [19]. Differences between men and women

371   appear to be more pronounced when evaluating longer term Orlistat treatment over 48 months. Over

372   this longer treatment period, the base case analysis reports higher cost per QALY for men (£29,089)

373   compared to women (£26,917). Within this analysis, for men, the data suggest that the greater the initial

374   BMI, the more cost-effective Orlistat is (ICER = £29,920; BMI = 38kg/m^2), with the ICER increasing

375   to £33,134 when initial BMI is 30kg/m^2. The converse appears to be true for women: ICER = £30,155

376   for an initial BMI = 38kg/m2; ICER = £23,982 for an initial BMI = 30kg/m^2. The results show that for

377   the comparison of 48 vs. 12 months' treatment with Orlistat, cost-effectiveness is dependent upon a

378   number of factors, including sex, baseline BMI, weight trend without Orlistat, and weight regain after

379   treatment discontinuation. The conclusion of the evaluation was that NICE could not recommend 48

380   months of treatment, given the uncertainty in the ICER presented. This appears to be the only publicly

381   available guidance internationally which highlights the cost-effectiveness of Orlistat specifically for

382   men.

383

384   ***Quality assessment of the included studies:***

385

386   The results of all the included studies should be interpreted in light of highly variable methodological

387   quality. All included studies were formally quality assessed according to the Phillip's critique for

388   economic evaluations [18]. Five studies used Markov models to extrapolate short term outcomes over

389   a longer time horizon and estimate cost-effectiveness [20] [21] [22] [24] [26], one used a discrete event

390   simulation model [25] to compare the time to development of obesity related complications and oneused

391   Cox regression modelling to estimate time to death as a measure of effectiveness [23]. However, the

392   latter only projected long term outcomes, not costs. This is an important omission from economic

393   studies as cost implications to health services are likely to occur far into the future, through differing

394   risks of developing health related complications and requiring expensive hospital care. The disease

395   states included in the modelling process varied depending on the study. The most common disease

396   states modelled were heart disease and diabetes. Given the many health related complications

397   associated with obesity and their chronic nature, Markov models and or discrete event simulation

398   models, which extrapolate both costs and outcomes over a long time horizon, including for diseases

399   other than heart disease and diabetes such as cancers and osteoarthritis, could be argued to give the most

400   appropriate estimate of cost-effectiveness.

401

402   While more sophisticated models are often preferred, it is also important to consider the underlying

403   processes, quality of the data used to populate the model and the underlying assumptions used to

404   estimate cost-effectiveness. Data used within the models were generally well described and clearly

405   referenced, though there is little evidence of formal systematic searching for data to populate the

406 models. Methods used to synthesize data from the literature to estimate model treatment effects were

407 poorly described. Only two studies detailed the meta-analysis carried out [20] [25].

408

409 The costing perspective was described in all studies. The most common perspective was that of the

410 health services, though two studies stated a societal perspective [20] [22] and one a social health

411 insurance perspective [26]. Intervention costs were included for all studies, and downstream costs to

412 health services included in six out of the seven. Despite their inclusion in the evaluations, the

413 calculation of intervention and downstream costs was not always thoroughly reported and prevented

414 reproducibility of the results. Where appropriate, costs were discounted to their present day values,

415 though only three studies tested the impact of varying discount rates on cost-effectiveness outcomes in

416 sensitivity analyses [20] [24] [25].

417

418 Effectiveness data used in the models were, for the most part, based on weight loss which was used to

419 predict clinical outcomes such as cholesterol levels, systolic blood pressure and HbA1c levels and taken

420 from published sources. However, the explicit modelled link between weight loss data and clinical

421 outcome measures has generally been poorly described. There is also little evidence to determine

422 whether model inputs were always based on sex-specific data. Whilst it is clear that the goal of

423 interventions modelled in the studies was to induce weight loss, and results were reported for men, the

424 methods of extrapolating weight loss to long term sex specific outcomes are not always clearly

425 presented. Indeed, weight loss data were poorly reported generally, with even less data presented on

426 differences in weight loss by sex.

427

428 Some studies used Framingham risk equations [31] [33] to determine relative risks of cardiovascular

429 events which were then linked, using a combination of literature and modelling exercises to final health

430 outcomes and complications (e.g. diabetes, stroke, myocardial infarction etc.). Again, this was

431 completed to varying degrees of complexity and data were not always clearly reported for weight loss

432 or gender specific model inputs. Studies which failed to clearly report model data inputs are very

433 difficult to generalise across groups, and would be theoretically difficult to re-produce in practice.

434

435 Three studies were cost-utility analyses [20] [22] [25], reporting results as cost per QALY gained. Such

436 studies may be of greatest value to decision makers as they combine quality and length of life in one

437 single outcome. Whilst the mortality (length of life) component was always well described, the methods

438 used to derive utility weights were less clear. This has important implications for the generalizability

439 of the results, particularly in an international context. One study reported cost per an average

440 effectiveness score developed by the authors to reflect the importance of different grades of weight loss

441 and the risk of developing obesity related complications [26]. The remaining three were cost-

442 effectiveness analyses, reporting cost per life year gained [21] [23] [24].

443

444 Assumptions regarding the duration and continuation of treatment effect, for example weight loss and

445 weight regain over time or changes in clinical risk factors (such as blood pressure) are crucial drivers

446 of cost-effectiveness of weight loss interventions. Galani and colleagues assumed that weight loss was

447 maintained over six years, with linear regain over four [20]. Therefore, after 10 years, it was assumed

448 weight had returned to baseline levels. This assumption was validated against the Finnish Diabetes

449 Prevention Study [29], however alternative assumptions were not explored in sensitivity analysis.

450 While mortality and cardiovascular risk factors are based on sex-specific data and these are extrapolated

451 to final outcomes, it is not clear if these were applied to sex-specific weight loss data or not. Maetzel

452 and colleaguesassumed that patients receiving Orlistat would have weight loss over one year of therapy

453 after which weight regain would be linear over three years, up to a point where weight would match

454 that of the placebo group [24]. This assumption was tested in the author's sensitivity analysis and was

455 found to have an important impact on cost-effectiveness results. The remaining studies did not

456 adequately document their assumptions about continuation of treatment effect over time. While such

457 information is likely to be uncertain, it is important that the impact of any assumptions is thoroughly

458 tested in sensitivity analyses.

459

460 All but one [26] of the studies attempted some form of sensitivity analysis, mainly focussing on issues

461 of parameter uncertainty. Heterogeneity in study results was well accounted for across studies, with

462   four out of five studies reporting results for key subgroups (e.g. impaired glucose tolerance (IGT), age

463   groups, sex). All studies reported cost-effectiveness results for men and women separately, the only

464   exception being Maetzel and colleagues [24], for which the base case model results were specific to

465   men. Subgroup analyses conducted were appropriate to the study question and were generally clearly

466   reported and interpreted. Where multi-variable sensitivity analyses were conducted, results were not

467   always reported separately for men and women. Three studies [20] [22] [24] conducted extensive

468   probabilistic sensitivity analysis, with uncertainty in cost-effectiveness estimates reported as cost-

469   effectiveness acceptability curves (CEACs) and scatter plots. Again, however, illustrations were only

470   reported for sex-specific subgroups in one study [20]. Comprehensive conduct of sensitivity analysis

471   is crucial to determine the strength of a study's conclusions as well as the degree to which the results

472   are generalizable to other setting, populations or countries.

473

474   A summary of the quality assessment for each study is provided in Table 3. More detailed comments

475   on quality assessment forms for individual studies are available from the authors on request.

476

477

478 **DISCUSSION**

479

480 To our knowledge, this is the only systematic review of studies which evaluate the cost-effectiveness of

481 interventions for the treatment of obesity in men. Although the studies retrieved offered some insights into

482 the potential differences in cost-effectiveness of treatments for men and women, especially in relation to

483 Orlistat, none of the studies specifically set out to determine sex specific cost-effectiveness results. As a

484 result, it is not always clear that model inputs were sex-specific. Further, as it was not an original objective,

485 no studies conducted the full range of sensitivity analyses on men and women separately. It was therefore

486 not possible to assess the full range of uncertainty in reported cost-effectiveness estimates for men and

487 women separately.

488

489 Our review does however provide some insights that these obesity treatments may offer good value for

490 money. This was particularly evident in studies which targeted the highest risk groups in society, such as

491 those with impaired glucose tolerance. Targeting these high risk groups could improve the cost-

492 effectiveness case of treatments further. However, there was insufficient evidence reported to determine

493 whether targeting at risk men had different cost-effectiveness outcomes from targeting at risk women.

494

495 Our review compliments a body of literature summarising the evidence on effectiveness and cost-

496 effectiveness of obesity interventions. Lehnert and colleagues [11] provide a review of the cost-

497 effectiveness literature, including studies which didn't report results separately for men and women. They

498 found, similarly to our review, that the majority of interventions were cost-effective, or cost-saving. This

499 complements the results of the studies included in our review. However caution should be noted when

500 interpreting the broad suggestion of cost-effectiveness, as whether or not an intervention is cost-effective

501 will be determined by the comparison which is made and the modelling for long-term weight loss

502 maintenance. Lehnert specifically found that modifications to a target population's environment through

503 fiscal and regulatory measures were the most cost-effective [11]. We found insufficient evidence to confirm

504   this conclusion in men only studies. However, this is an area which warrants future research in men.

505   Similarly to our review, Lehnert also found large uncertainty in reported cost-effectiveness results. This

506   renders it difficult to draw firm conclusions. Further, study heterogeneity of interventions, comparators,

507   modelling techniques, disease states considered and time horizon of costs and outcomes further complicate

508   judgements about the comparative cost-effectiveness of interventions.

509

510   Our review concluded that there was a paucity of literature on the cost-effectiveness of non-surgical

511   interventions to manage obesity in men. A recently published study reporting clinical outcome results,

512   suggests that a community delivered intervention targeted at obese and overweight men in 13 Scottish

513   professional football clubs offers promising results. The Football Fans In Training (FFIT) intervention [35]

514   may also be a cost-effective use of resources, based on a preliminary economic evaluation presented in the

515   trial results. However, in order to definitively determine cost-effectiveness we await the publication of

516   results from the long term modelling exercise linked to this study.

517

518   Our review was conducted to address the cost-effectiveness of lifestyle and drug interventions to treat

519   obesity in men. Nonetheless, surgery represents an important part in the obesity treatment pathway and is

520   worthy of discussion. There are clear differences in the provision of bariatric surgery depending on sex.

521   For example, in England in 2009 / 2010 obesity surgery was more common among women (5047

522   procedures) than men (1473 procedures) [36].   Obesity surgery has been found to be clinically and cost-

523   effective [37, 38] and may even generate long term cost savings to health services providers in terms of

524   reduced hospital contacts over a longer period of time [39]. Although there is good evidence on cost-

525   effectiveness of bariatric surgery in the most obese population groups, the authors are unaware of any strong

526   evidence relating to sex-specific cost-effectiveness. Determining whether or not there is a sex-specific

527   element to the cost-effectiveness of obesity surgery, and if so what the drivers of this difference may be,

528   are important avenues for future research. Robust evidence is required to determine if the current imbalance

529   in provision of surgery by sex in the UK is a cost-effective use of scarce health services resources.

530

531   Whilst the studies included in our review point towards the cost-effectiveness of weight loss interventions,

532   they should however be interpreted with caution and in light of their methodological limitations. Studies

533   included were not explicitly designed to evaluate cost-effectiveness in men alone and it was thus not

534   possible to fully evaluate the applicability of reported results to men only subgroups. For example, it was

535   not always clear if data inputs were sex-specific and it was uncommon for uncertainty in men only analyses

536   to be reported in detail. This renders it difficult to draw strong conclusions or provide guidance to policy

537   makers interested in sex specific policy questions.

538   In terms of guidance for future good practice economic evaluation research, our review noted many strong

539   and important assumptions regarding modelling of the continuation of treatment effect and weight loss

540   maintenance over time across the studies, with no clear consensus on how this has been incorporated into

541   the respective economic models. Studies which assume maintenance of incremental weight loss over time

542   for the experimental group are likely to bias the analysis greatly in favour of the experimental intervention.

543   Studies which conducted sensitivity analysis on assumptions around continuation of treatment effect over

544   time, showed substantial variation in the presented ICERs. There is a clear lack of evidence on continuation

545   of treatment effect to inform the models, however it is important that adequate sensitivity analyses are

546   presented in order to fully inform decision makers regarding uncertainty in this important model parameter.

547   Maintenance of treatment effect is likely to be determined mainly through adherence to lifestyle changes

548   introduced at early stages of an intervention. Adherence to health lifestyle is an important driver of cost-

549   effectiveness and one which has received insufficient coverage in the literature in general. Reviews of

550   clinical effectiveness and qualitative literature conducted in parallel to this review address alternative

551   measures which can motivate men and encourage adherence to interventions [13]. Engaging participants

552   with interventions being tested and ensuring adherence to the therapy under evaluation is a key component

553   of determining an interventions effectiveness, and hence its cost-effectiveness. Failure to engage

554   participants in weight loss interventions can have a substantial impact on healthcare resource use, especially

555   when rolled out to a large population of overweight or obese individuals. The impact on cost-effectiveness

556 can be substantial, yet only one study in our review addressed the issue of adherence [25], finding that

557 results were sensitive to the percentage of participants who fully adhered to the weight loss programme.

558

559 The framework of the analysis is a further important point to consider in economic evaluation. Cost-Utility

560 analyses, reporting cost per QALY tend to be the gold standard for economic evaluation. The advantage

561 of using QALYs is that they can improve the comparability of studies, and can thus be used to aid policy

562 makers regarding resource allocation decisions. While QALYs are commonly used for this purpose, and

563 are recommended by NICE, they only capture the health benefits of an intervention. There is scope for

564 future research to consider broader measures of value, perhaps in the form of cost benefit analyses, which

565 capture and include benefits associated with care processes and non-health outcomes. The inclusion of

566 broader, preference based measures of outcome, such as discrete choice experiments (DCEs), can help to

567 generate information on what is important to patients, and what they value most. DCEs can be used to

568 determine the attributes of the processes and outcomes of care that are important to individuals, thus helping

569 to improve adherence and weight loss maintenance. They can also be used in a cost-benefit analysis

570 framework.

571

572 There is an urgent need for high quality economic evaluations, addressing a research question on cost-

573 effectiveness of obesity related interventions for men. The long term economic results from the FFIT study

574 [35] will undoubtedly be an important contribution to this literature. However, the target group is limited

575 to football fans. Further high quality studies are required to assess the value for money of other targeted

576 weight loss interventions for men. Such studies should systematically consider the available evidence on

577 acceptability, effectiveness and costs associated with alternative interventions. Future research studies

578 should be based on decision analytical models, with sex-specific model input data. Further consideration

579 should be given to the methods used to link the effect of weight loss to overall disease risk. Some of our

580 included studies seemed to suggest that small and even transient weight loss may have an impact on future

581 disease risk and therefore could have an important impact on long-term effectiveness and cost-effectiveness

582   outcomes. Maintenance of weight loss over time is an important parameter for cost-effectiveness and

583   should be comprehensively tested in sensitivity analyses, with appropriate ranges of cost-effectiveness

584   presented to decision makers. In this regard, studies should explicitly consider preferences of individual

585   groups of the population to develop targeted ways in which to improve adherence and encourage long term

586   maintenance of weight loss. This too will have important consequences for cost-effectiveness outcomes.

587

588   **CONCLUSION**

589

590   Our review did not identify any studies which evaluated the long term cost-effectiveness of weight loss

591   interventions designed explicitly for men. However, the long-term economic results from the FFIT study

592   [35] will help to begin to bridge a gap in this literature. There is some evidence that lifestyle interventions

593   combining low fat (usually reducing), dietary advice and physical activity are likely to be cost-effective,

594   and that Orlistat may be cost-effective in addition to a lifestyle intervention, especially when targeted at

595   those with or at greatest risk of developing type 2 diabetes (e.g. those with IGT). However, there were no

596   clear or systematic differences in cost-effectiveness of any of the interventions between men and women.

597   There was insufficient evidence to draw strong conclusions on cost-effectiveness of weight loss

598   interventions in men. Future studies should develop interventions which specifically target men. Economic

599   evaluations should ensure that analyses are modelled over a sufficiently long time horizon to capture the

600   most important costs and health outcomes attributable to weight loss interventions. Researchers are

601   recommended to follow best practice guidelines for the conduct of economic evaluations alongside

602   randomized controlled trials [40] and modelling studies [18]. Following specific best practice guidelines

603   will improve the evidence base on cost-effectiveness and ensure the best quality economic evidence is

604   provided to policy makers targeting weight loss in men.

605

606

607 **REFERENCES**

[1]   Centres for disease control and prevention. Healthy weight, overweight and obesity among adults

        aged 20 and over, by selected characteristics: United States, selected years 2007-2010 (2012).

        [Online]. Available: http://www.cdc.gov/nchs/data/hus/2012/068.pdf. [Accessed February 2014].

[2]   The Health and Social Care Information Centre. Health Survey for England - 2011, Health,

        social care and lifestyles (2012). [Online]. Available:

        http://www.ic.nhs.uk/searchcatalogue?productid=10149&returnid=1685. [Accessed February

        2014].

[3]   Butland B, Jebb S, Kopelman P, McPherson K, Thomas S, Mardell J, Parry V. Foresight.

        Tackling Obesities: Future Choices - Project Report 2nd edition. (2007). [Online]. Available:

        http://www.bis.gov.uk/assets/foresight/docs/obesity/17.pdf. [Accessed February 2014].

[4]   Bradshaw P, Bromley C, Corbett J, et al. The Scottish Health Survey, Volume 1: Adults. (2012).

        [Online]. Available: www.scotland.gov.uk/Resource/0040/00402630.pdf. [Accessed February

        2014].

[5]   Finucane M, Stevens G, Cowan M, et al. National, regional and global trends in body mass index

        since 1980: systematic analysis of health examination surveys and epidemiological studies with

        960 country years and 9.1 million participants. *Lancet* 2012; **377:** 557-67.

[6]   Ross R, Shaw K, Rissanen J, Martel Y, De Guise J, Avruch L. Sex differences in lean and

        adipose tissue distribution by magnetic resonance imaging: Anthropometric relationships. *Am J

        Clin Nutr* 1994; **59:** 1277-85.

[7]   Han T, Tajar S, O'Neill T, et al. Impaired quality of life and sexual function in overweight and

        obese men: the European Male Ageing Study. *Eur J Endocrinol* 2011; **164**: 1033-11.

[8]   Wang Y, McPherson K, Marsh T, Gortmaker S, Brown M. Health and economic burden of the

        projected obesity trends in the USA and the UK. *Lancet* (2011); **378:** 815-25.

25

[9] McPherson K, Marsh T, Brown M. Foresight. *Tackling obesity: future choices - modelling future trends in obesity and their impact on health*. London: Government Office for Science, 2007.

[10] Flegal K, Carroll M, Ogden C, Curtin L. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA* 2010; **303**: 235-41.

[11] Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, Konig H. The long term cost-effectiveness of obesity prevention interventions: systematic literature review. *Obesity Reviews* 2012; **13**: 537-53.

[12] Avenell A, Broom J, Brown T, et al. Systematic review of the long-terms effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess* 2004; **8** (21)**.**

[13] Robertson C, Archibald D, Avenell A, Douglas F, Hoddinott P, van Teijlingen E, Boyers D, Stewart F, Boachie C, Fioratou E, Wilkins D, Street T, Carroll P, Fowler C. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. *Health Technol Assess* 2014; 18(35):1-424

[14] Pagoto SL, Schneider KL, Oleski JL, Luciani JM, Bodenlos JS, Whited MC. Male inclusion in randomized controlled trials of lifestyle weight loss interventions. *Obesity* 2012;**20**:1234-9.

[15] Eurostat. *Annual Average inflation rates, 2001-2014*. European Commission, 2014. [Online]. Available: http:// ec.europa.eu/eurostat/web/hicp/data/database. [Accessed Janurary 2015].

[16] Historical Inflation Rates for Australia. (2014). [Online]. Available: http://www.rateinflation.com/inflation-rate/australia-historical-inflation-rate. [Accessed Janurary 2015].

[17] Organisation for Economic Co-operation and Development. *Prices and purchasing power parities (PPP)*. OECD: Paris, 2013. [Online]. Available: http://www.oecd.org/std/pricesandpurchasingpowerparitiesppp/. [Accessed February 2014].

[18]   Phillips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision analytic modelling in health technology assessment. *Health Technol Assess* 2004; **8** (36).

[19]   National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. (2008). [Online]. Available: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf. [Accessed February 2014].

[20]   Galani C, Schneider H, Rutten F. Modelling the lifetime costs and health effects of lifestyle intervention in the prevention and treatment of obesity in Switzerland. *Int J Public Health* 2007; **52**:372-82.

[21]   Segal L, Dalton A, Richardson J. Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promot Int* 1998; **13**: 197-209.

[22]   Ianazzo S, Zaniolo O, Pradelli L. Economic evaluation of treatment with orlistat in Italian obese patients. *Curr Med Res Opin* 2008; **24**: 63-74.

[23]   Olsen J, Williang I, Ladelund S, Jorgensen T, Gundgaard J, Sorensen J. Cost-effectiveness of nutritional counselling for obese patients and patients at risk of ischemic heart disease. *Int J Technol Assess Health Care* 2005; **21**: 194-202.

[24]   Maetzel A, Ruof J, Covington M, Wolf A. Economic evaluation of orlistat in overweight and obese patients with type 2 diabetes mellitus. *Pharmacoeconomics* 2003; **21**: 501-12.

[25]   Miners A, Harris J, Felix L, Murray E, Michie S, Edwards P. An economic evaluation of adaptive e-learning devices to promote weight loss via dietary change for people with obesity. *BMC Health Services Research* 2012; **12:**190

[26]   Spyra A, Riese A, Rychlik R. Cost-effectiveness of different programs for weight reduction in obese patients with diabetes. *Gesundheitsokönomie & Qualitätsmanagement* 2014; **19**: 79-84

[27] National Institute for Health and Care Excellence. *Review of Clinical Guideline (CG43) - Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children*. (2011). [Online]. Available: http://www.nice.org.uk/nicemedia/live/11000/57615/57615.pdf. [Accessed February 2014].

[28] National Institute for Health and Care Excellence. *Public Health Guidance [PH53] – Managing overweight and obesity in adults – lifestyle weight management services*. (2014). [Online]. Available: http://www.nice.org.uk/guidance/PH53. [Accessed January 2015]

[29] Lindstrom P, Peltonen M, Tuomilehto J. Lifestyle strategies for weight control: experience from the Finnish Diabetes Prevention Study. *Proc Nutr Soc* 2005; **64:** 81-8.

[30] Torgerson J, Hauptman J, Boldrin M, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27**: 155-61.

[31] Stratton I, Adler A, Neil H, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321** (7258): 405-12.

[32] McConnon A, Kirk S, Cockroft J, Harvey E, Greenwood D, Thomas J, Ransley J, Bojke L. The internet for weight control in an obese sample: Results of a randomised controlled trial. *BMC Health Services Research* 2007; **7**: 206

[33] Anderson K, Odell P, Wilson P, Kannel W. Cardiovascular disease risk profiles. *Am Heart J* 1991;**121:** 293-8.

[34] National Institute for Health and Care Excellence. *TA22: Orlistat for the treatment of obesity in adults*. NICE: London, 2001.

[35] Hunt K, Wyke S, Gray C, et al. A gender sensitised weight loss and healthy living programme for overweight and obese men delivered by Scottish Premier League football clubs (FFIT): a

pragmatic randomised controlled trial. *Lancet* 2014; [Online]. Available:

http://dx/dpo.org/10.1016/S014-6736(13)62420-4.

[36]   Dent M, Chrisopoulos S, Mulhall C, Ridler C. Bariatric surgery for obesity. Oxford: National

Obesity Observatory, 2010.

[37]   Picot J, Jones J, Colquilt J. The clinical and cost-effectiveness of bariatric (weight loss) surgery

for obesity: A systematic review and economic evaluation.

[38]   Dixon J, Zimuet P, Albertit G, Rubino F. Bariatric surgery: an IDF statement for type 2 diabetes.

2011 Diabet Med 28 628-42

[39]   Crimieux P, Buchwald H, Shikora S, Ghash A, Yang H, Bussing M, A study on the economic

impact of bariatric surgery. Am J Manag Care 2008 14: 589-596

[40]   Drummond M, Jerrerson T. Guidelines for authors and peer reviewers of economic submissions

to the BMJ. The BMJ Economic working party. *BMJ* 1996; **313** (7052): 275.

608

609

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 ≥27kg/m^2 (overweight) or BMI score of ≥ 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≥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.

Study	Country	Population group evaluated	Sex breakdown	Study Setting	Description of Intervention	Description of control / comparison
					provided, especially to those not visiting the site often. 12 months subscription to site.	
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) <u>Body-Med nutrition concept:</u> 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) <u>MOBILIS Programme:</u> 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) <u>DGE ('I am Losing Programme'):</u> 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) <u>Therapeutic Nihilism:</u> 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.

611 *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
612 included.
613 ** ATG = adherence to guidelines; standard pharmacotherapy for type 2 diabetes (e.g. metformin) and weight management (diet and physical activity)
614 *ATG = Adherence to Guidelines; BMI = Body Mass Index; DGE: Deutsche Gesellschaft für Ernählung (translated from German as the German Society for*
615 *Nutrition); GP = General Practitioner; Mg. = Milligrams; Mins = Minutes; MOBILIS: Multizentrisch Organisierte Bewegungsorientierte Initiative zur*
616 *Lebensstiländerung In Selbstverantwortung (translated from German as a Multi-centre movement oriented initiative for lifestyle change through self-*

617 *responsibility); NR = Not Reported; UKPDS = United Kingdom Prevention of Diabetes Study; XENDOS = XENical for the preventions of Diabetes in Obese*
618 *Subjects.*
619

620 **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

621   [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*
622   *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*
623   *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*

624   *calculations. Data reported for ICERs are as reported in the studies. B/L = Borderline; CHF= Swiss Francs; DGE: Deutsche Gesellschaft für Ernählung*
625   *(translated from German as the German Society for Nutrition); GBP = Great British Pounds; GP = General Practitioner; ICER = Incremental cost-*
626   *effectiveness ratio; IGT= Impaired Glucose Tolerance; Inc. = Incremental; M= Men; MOBILIS: Multizentrisch Organisierte Bewegungsorientierte Initiative zur*
627   *Lebensstiländerung In Selbstverantwortung (translated from German as a Multi-centre movement oriented initiative for lifestyle change through self-*
628   *responsibility); N/A = Not applicable; NR = Not Reported; OB = Obese; O/W = overweight; QALY = Quality Adjusted Life Year; USD = US dollars; W =*
629   *Women; WTP = Willingness to Pay*
630

631

632 **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

			Galani 2007 [19]	Ianazzo 2008 [21]	Maetzel 2003 [23]	Olsen 2005 [22]	Segal 1998 [20]	Miners 2012 [25]	Spyra 2014 [26]
		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	?

Quality Criterion	Dimension of Quality	Question	Galani 2007 [19] Response Y/N/NA/?	Ianazzo 2008 [21] Response Y/N/NA/?	Maetzel 2003 [23] Response Y/N/NA/?	Olsen 2005 [22] Response Y/N/NA/?	Segal 1998 [20] Response Y/N/NA/?	Miners 2012 [25] Response Y/N/NA/?	Spyra 2014 [26] Response Y/N/NA/?
		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
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	?

Quality Criterion	Dimension of Quality	Question	Galani 2007 [19]	Ianazzo 2008 [21]	Maetzel 2003 [23]	Olsen 2005 [22]	Segal 1998 [20]	Miners 2012 [25]	Spyra 2014 [26]
		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

Quality Criterion	Dimension of Quality	Question	Galani 2007 [19]	Ianazzo 2008 [21]	Maetzel 2003 [23]	Olsen 2005 [22]	Segal 1998 [20]	Miners 2012 [25]	Spyra 2014 [26]
		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

Quality Criterion	Dimension of Quality	Question	Galani 2007 [19]	Ianazzo 2008 [21]	Maetzel 2003 [23]	Olsen 2005 [22]	Segal 1998 [20]	Miners 2012 [25]	Spyra 2014 [26]
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

633

634

635

636

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

638 MEDLINE (1946 to 24 October 2014);

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

640 EMBASE (1974 to October 2014)

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

642

643 1. exp "costs and cost analysis"/

644 2. cost-benefit analysis/

645 3. quality-adjusted life years/

646 4. economics,pharmaceutical/

647 5. exp budgets/

648 6. exp models, economic/

649 7. exp decision theory/

650 8. monte carlo method/

651 9. markov chains/

652 10. exp health status indicators/

653 11. cost$.ti.

654 12. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.

655 13. economic$ model$.tw.

656 14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw.

657 15. (price$ or pricing).tw.

658 16. (financial or finance or finances or financed).tw.

659 17. ((value adj2 money) or monetary).tw.

660 18. markov$.tw.

661 19. monte carlo.tw.

662 20. (decision$ adj2 (tree? or analy$ or model$)).tw.

663 21. (standard adj1 gamble).tw.

664 22. trade off.tw.

665 23. or/1–22

666 24. *obesity/

667 25. *overweight/

668 26. obesity, morbid/ use prmz

669 27. morbid obesity/ use oemez

670 28. (obes$ or overweight).tw.

671 29. weight loss/ use prmz

672 30. weight reduction/ use oemez

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

674 32. (obesity adj1 management).tw.

675 33. (anti obesity or antiobesity).tw.

676 34. or/24–32

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

678 36. *obesity/ec

679 37. *overweight/ec

680 38. or/36-37

681 39. (women not men).tw.

682 40. (female not male).tw.

683 41. 38 not (39 or 40)

684 42. 23 and 34 and 35

685 43. 41 or 42

686 44. exp animals/ not humans/

687 45. 43 not 44

688 46. (rat or rats).tw.

689   47. 45 not 46

690   48. limit 47 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "all adult (19 plus years)"

691   or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5

692   years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

693   49. limit 47 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12

694   years>or adolescent <13 to 17 years>)

695   50. 47 not 48

696   51. 47 not 49

697   52. 50 or 51

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

699   54. remove duplicates from 53

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

701   56. 54 not 55

702

703