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1 **How effective are weight loss interventions for improving fertility in women and men**  
2 **who are overweight or obese? A systematic review and meta-analysis of the evidence.**

3 **Authors:** Damian Best<sup>1</sup>, Alison Avenell<sup>2</sup>, Siladitya Bhattacharya<sup>1</sup>

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12 **Running title:** Do weight loss interventions improve fertility?

13 **AUTHOR:** there is a limit of 50 characters for the running title. [Is this alternative acceptable?](#)

14

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16 Table of Contents

17 **AUTHOR:** the table of contents does not appear to agree with the text. Only first (e.g.  
18 **Introduction, Methods**) and second level headings (e.g. *Criteria for considering studies for*  
19 *this review*) can be included in the Table of Contents (although third etc. level headings are  
20 allowed in the main text). The styles used for headings in the main text should be consistent  
21 and only second level headers included here. Please would you recheck and edit both the  
22 main text and Table of Contents accordingly? Thank you.

23 Abstract

24 Introduction

25 Methods

26 Criteria for considering studies for this review

27 Search methods for identification of studies

28 Data collection and analysis

29 Assessment of risk of bias in individual studies

30 Summary measures

31 Synthesis of results

32 Assessment of heterogeneity

33 Sensitivity analyses

34 Results

35 Outcome of the search

36 Description of populations

37 Description of interventions

38 Quality of studies

39 Studies involving female infertility participants

40 Comparisons with metformin

41 Barriers to weight loss in infertile women

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42 Studies involving male infertility participants

43 Discussion

44 Conclusions

45

46 **Abstract**

47

48 **BACKGROUND**

49 The prevalence of obesity is increasing worldwide, with a corresponding increase in overweight  
50 and obese patients referred with infertility. This systematic review aimed to determine whether  
51 non-surgical weight reduction strategies result in an improvement in reproductive parameters  
52 affected by obesity, e.g. delayed time to pregnancy, oligozoospermia and azoospermia. No prior  
53 reviews have examined this within the general fertility population, or in both sexes.

54

55 **OBJECTIVE AND RATIONALE**

56 Our objective was to answer the question: "In overweight and obese women, men and couples  
57 seeking fertility treatment, what non-surgical weight loss interventions have been used, and  
58 how effective are they at weight loss and improving reproductive outcomes?"

59

60 **SEARCH METHODS**

61 An electronic search of MEDLINE, EMBASE and the Cochrane Library was performed for studies  
62 published between [AUTHOR: correct?] January 1966 and March 2016. Text word and MESH  
63 search terms used related to infertility, weight, and barriers to weight loss. Inclusion criteria  
64 were: an intervention to change lifestyle evaluated in any study design in participants of either  
65 gender with an unfulfilled desire to conceive. Studies were excluded if they included  
66 participants not attempting pregnancy, with illnesses that might cause weight fluctuations, or  
67 studies evaluating bariatric surgery. Two reviewers performed data extraction and quality

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68 assessment using the Cochrane Risk of Bias Tool for randomised trials, and a ratified checklist  
69 (ReBIP) for non-randomised studies.

70

#### 71 **OUTCOMES**

72 A total of 40 studies were included, of which 14 were RCTs. Primary outcomes were pregnancy,  
73 live birth rate and weight change. In women, reduced calorie diets and exercise interventions  
74 were more likely than control interventions to result in pregnancy [Risk Ratio 1.59, 95% CI  
75 (1.01, 2.50)], and interventions resulted in weight loss and ovulation improvement, where  
76 reported. Miscarriage rates were not reduced by any intervention.

77

#### 78 **WIDER IMPLICATIONS**

79 Overweight and obese persons seeking fertility should be educated on the detrimental effects of  
80 fatness and the benefits of weight reduction, including improvement in pregnancy rates. A  
81 combination of a reduced calorie diet, by reducing fat and refined carbohydrate intake, and  
82 increased aerobic exercise should form the basis of programmes designed for such individuals.  
83 A lack of randomised studies in men and couples, and studies evaluating barriers to undertaking  
84 weight loss in infertile populations is evident, and future research should examine these issues  
85 further.

86

87 **Key words:** infertility, obesity, weight loss, systematic review, diet, exercise

88 **Introduction**

89

90 Overweight is defined by the World Health Organization (WHO) (World Health Organization,  
91 2016) as a BMI  $\geq 25$  kg/m<sup>2</sup>, and obesity as  $\geq 30$  kg/m<sup>2</sup>. The prevalence of obesity is increasing  
92 worldwide (World Health Organization, 2016), with more than 600 million obese adults,  
93 including 15% of women, in 2014 - double the prevalence reported three decades earlier.

94 Infertility is defined by the failure to achieve a clinical pregnancy after 12 months or more of  
95 regular unprotected sexual intercourse (Zegers-Hochschild *et al.*, 2009; National Institute for  
96 Health and Clinical Excellence, 2013). Using this definition, infertility affects about 1 in 7  
97 couples in the UK, which is similar to an estimate of prevalence in the USA (Thoma *et al.*, 2013).

98 An increasingly overweight and obese population has led to a greater proportion of individuals  
99 with high BMI being evaluated in infertility settings (Vahratian and Smith, 2009).

100

101 BMI has been associated with delayed conception in women in a dose-dependent fashion  
102 (Gesink Law *et al.*, 2007; Wise *et al.*, 2013; Wise *et al.*, 2010). It is thought to produce  
103 anovulation (Zain and Norman, 2008; Klenov and Jungheim, 2014), which results in menstrual  
104 irregularity (Hartz *et al.*, 1979; Zain and Norman, 2008); impairment of oocyte development  
105 (Klenov and Jungheim, 2014) and quality (Carrell *et al.*, 2001; Metwally *et al.*, 2007); and it also  
106 has direct effects on the endometrium (Bellver *et al.*, 2011). With ovulation induction (OI)  
107 treatment, higher doses of medications (Dickey *et al.*; Balen *et al.*, 2006a) and a longer period of  
108 stimulation (Balen *et al.*, 2006b) are required with a higher BMI. With IVF, the chances of  
109 achieving a pregnancy decrease with each unit increase in BMI (Ferlitsch *et al.*, 2004), and it is  
110 thought that implantation rates are lower in obese women (Bellver *et al.*, 2010; Styne-Gross *et*  
111 *al.*, 2005). An increased risk of miscarriage following IVF has also been reported (Maheshwari  
112 *et al.*, 2007).

113

114 Obesity may affect male fertility in a dose-dependent manner (Sallmen *et al.*, 2006). Postulated  
115 mechanisms include increased testicular temperature with prolonged sitting (Hammoud *et al.*,  
116 2012), and increased oestrogen production in fat with disruption of the hypothalamo-pituitary-  
117 gonadal axis (Schneider *et al.*, 1979; Shukla *et al.*, 2014). Some studies have suggested reduced  
118 sperm concentration and motility (Hammiche *et al.*, 2012; Hakonsen *et al.*, 2011; Sermondade  
119 *et al.*, 2013), and lower clinical pregnancy rates with IVF (Keltz *et al.*, 2010; Umul *et al.*, 2015)  
120 with increasing male adiposity. Where both partners are obese, greater difficulty achieving  
121 pregnancy is expected (Ramlau-Hansen *et al.*, 2007).

122

123 Patients attending for fertility treatments are often advised to optimize their weights to  
124 improve outcomes, and in some cases to access assistance with funding (National Institute for  
125 Health and Clinical Excellence, 2013; Farquhar and Gillett, 2006; Infertility Network UK, 2015)  
126 or to reduce the risks of obstetric complications (The Royal Australian and New Zealand College  
127 of Obstetricians and Gynaecologists, 2011).

128

129 The purpose of this systematic review was to investigate first whether weight loss interventions  
130 for infertile patients achieve their goal in reducing weight, and second whether they result in  
131 improved fertility outcomes. A prior systematic review of 11 studies in women (Sim K.A. *et al.*,  
132 2014) focussed on assisted reproduction only and used a much more limited search for studies  
133 up until 2014. Our review used an extensive search until 2016 and presents data from 40  
134 studies with women and men with infertility, not just patients requiring assisted reproduction.

135

136 **Methods**

137

138 This systematic review was undertaken according to a pre-specified protocol.

139

140 ***Criteria for considering studies for this review***

141

142 *Types of studies*

143 We included intervention studies in overweight or obese participants with any design and any  
144 duration of follow-up.

145

146 *Types of participants*

147 Participants could be of either sex. They were required to have both infertility, defined by an  
148 unfulfilled desire to conceive of any duration or attendance for infertility investigations or  
149 treatment, and a prescribed period of attempt at weight loss. A BMI  $\geq 25$  kg/m<sup>2</sup> was used to  
150 define overweight, and  $\geq 30$  kg/m<sup>2</sup> to define obesity (World Health Organization, 2016);  
151 participants were required to be at least overweight. Morbid obesity was defined by BMI  $\geq 40$   
152 kg/m<sup>2</sup>. Studies were excluded if participants were not actively attempting pregnancy, or had an  
153 illness or eating disorder that might result in weight fluctuation.

154

155 *Types of interventions*

156 Any intervention for weight loss allowed inclusion, for example prompt for weight reduction,  
157 dietary modification, exercise, psychological or behavioural counselling, or the drug orlistat.  
158 Bariatric surgery was not included. Alternative or control interventions were included where  
159 evaluated in included studies.

160

161 *Types of outcome measures*



162 Primary outcomes were weight change, achievement of pregnancy, and live birth, the latter  
163 defined as the complete expulsion or extraction from its mother of a product of fertilisation,  
164 which, after such separation, breathes or shows any other evidence of life such as heart beat,  
165 umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether  
166 the umbilical cord has been cut or the placenta is attached (National Institute for Health and  
167 Clinical Excellence, 2013).

168  
169 Secondary outcomes were BMI change; waist circumference change (North American  
170 Association for the Study of Obesity *et al.*, 2000); miscarriage, defined as a loss of pregnancy  
171 before 23+6 weeks of gestation (Anonymous , 2012); ovulation improvement, with anovulation  
172 defined by suboptimal rise in LH, or a below-threshold serum progesterone level taken in the  
173 mid-luteal phase of the menstrual cycle (National Institute for Health and Clinical Excellence,  
174 2013); improvement in menstrual regularity, with irregular cycles defined as outside the range  
175 of 26-36 days (National Institute for Health and Clinical Excellence, 2013); and time to  
176 conception.

#### 178 ***Search methods for identification of studies***

179  
180 The dates searched were 1 January 1966 to 19 March 2016. No restriction was placed on  
181 language of origin, ~~or publication status~~ and studies could be included regardless of whether  
182 they had been published **(AUTHOR: please would you clarify what you mean by 'status' here?)**.

183 The electronic databases used were MEDLINE, EMBASE and the Cochrane Library. Additional  
184 studies were identified through review of the references of the retrieved papers, contact with  
185 study authors, and online searching of Google and Google Scholar (Google Inc., Mountain View,  
186 CA, USA). The search strategy used for MEDLINE and EMBASE is given in the **Supplementary**  
187 **Data (AUTHOR: we tend not to include Appendices, therefore these data have been divided and**  
188 **renamed as supplementary files.)**.

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189

190 **Data collection and analysis**

191

192 *Selection of studies*

193 The titles and abstracts obtained were screened by one author (DB). To verify the process of  
194 selection, the titles and abstracts for the year 2000 were independently screened by DB and AA,  
195 with full agreement with respect to papers to be included or excluded. Thus full text versions of  
196 all relevant papers were retrieved by DB for further scrutiny by both reviewers. Any  
197 disagreement between the two as to which studies to include was resolved by discussion.

198

199 *Data collection process*

200 Data were extracted by one reviewer (DB), and checked by a second (AA). Discrepancies were  
201 resolved by discussion between the reviewers, and a third reviewer (SB) was available for  
202 referral as necessary. Study authors were contacted as required for missing data or clarification.

203

204 For each included study, the information collected included study design; methods; location,  
205 setting and time period; information about the participants (demographics, infertility diagnosis,  
206 BMI, eligibility criteria); drop-outs; the types of interventions assessed and their descriptions;  
207 and outcomes, including pregnancy, live births, weight or BMI change, miscarriage, ovulation  
208 and menstrual change. For men, semen analysis parameters were captured. (AUTHOR: please  
209 would you re-state those outcomes here, for clarity? Thank you.) Any data on barriers to weight  
210 loss were also captured. Data on costs and cost-effectiveness were sought but not found.

211

212 *Assessment of risk of bias in individual studies*

213 RCTs were assessed for their methodological quality using the Cochrane Risk of Bias Tool  
214 (Higgins *et al.*, 2011).

215

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216 Non-randomised studies were assessed using a checklist developed for the Review Body for  
217 Interventional Procedures (ReBIP) (64) (AUTHOR: please would you use the correct format  
218 citation?). The ReBIP is an independent review body that carries out systematic reviews for the  
219 National Institute for Health and Care Excellence's Interventional Procedures Programme. The  
220 checklist was adapted from several sources (Verhagen *et al.*, 1998; Khan *et al.*, 2001; Downs  
221 and Black, 1998), and has been used in many systematic reviews. It includes assessment of  
222 sample selection; clarity of inclusion and exclusion criteria; baseline comparability of  
223 participants; consecutive selection of patients; prospective data collection; clarity of  
224 intervention descriptions; experience of person administering the intervention;  
225 appropriateness of staff, place and facilities where participants were treated; consideration of  
226 important incomes on clinical effectiveness, cost-effectiveness, or learning curves; use of  
227 objective outcome measures; blinding of outcome assessment; adequacy of duration of follow-  
228 up to detect important effects on outcomes of interest; information provision on dropouts, and  
229 their similarity to completers; identification of important prognostic factors; and adjustment of  
230 analyses for confounding factors.

231

### 232 *Summary measures*

233 Results were summarised descriptively. In the outcome summary tables, numbered rankings  
234 are provided in an effort to demonstrate which study interventions reported more favourable  
235 outcomes, with a lower number indicating a better outcome. Meta-analysis was undertaken  
236 where possible. Risk ratios (RR) and mean differences with 95% CI between groups are  
237 reported.

238

### 239 *Synthesis of results*

240 Data were imported into Review Manager Version 5.3.5 (The Cochrane Collaboration, Oxford,  
241 UK) for quantitative synthesis. A random effects, rather than a fixed effect model, was used for

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242 meta-analysis, owing to unavoidable population and intervention heterogeneity, as anticipated  
243 in interventions for weight loss.

244

245 *Assessment of heterogeneity*

246 Statistical heterogeneity was investigated by visual inspection of forest plots, the Q-test (with  
247  $p < 0.1$  implying statistical heterogeneity) and by examining the  $I^2$  statistic (Higgins and  
248 Thompson, 2002), where a result  $> 50\%$  was taken to indicate substantial statistical  
249 heterogeneity.

250

251 *Sensitivity analyses*

252 Sensitivity analysis was planned to compare randomised trials judged to be at low risk of bias  
253 for allocation concealment or randomisation with those judged to be at higher risk of bias;  
254 however, the small numbers of trials precluded this.

255 **Results**

256

257 ***Outcome of the search***

258

259 Details of the selection process for studies is summarised in the PRISMA flow diagram (Figure

260 1) **(AUTHOR: the quality of this figure still seems poor. If possible, please can you send to me a**

261 **higher quality file?** Seventeen study authors were contacted for clarification or further

262 information; ten provided helpful further information.

263

264 Full details of all the studies and interventions are provided in Supplementary Table SI. There  
265 were 14 RCTs, six non-randomised studies with comparison groups (NRCTs), and twenty cohort  
266 studies with interventions. Ten studies took place in Australia, seven in the USA, three each in  
267 Italy and the Netherlands, and two in Denmark. One each came from Belgium, Brazil, Canada,  
268 Egypt, France, Germany, India, Iran, Jordan, Pakistan, Russia, Saudi Arabia, Slovakia, Turkey and  
269 the UK. Three studies were multi-centre.

270

271 Enrolment varied from eight participants (Faure *et al.*, 2014) to 577 (Mutsaerts *et al.*, 2016).

272 Attrition rates ranged from 10.6% (Mutsaerts *et al.*, 2016) to 66.7% (Turner-McGrievy *et al.*,  
273 2014).

274

275 ***Description of populations***

276

277 Mean age of study groups varied from 25 years (Lazurova *et al.*, 2004) to 35.4 years (Chavarro  
278 *et al.*, 2012). Ethnicity was reported in six papers, with between 55% (Turner-McGrievy *et al.*,  
279 2014) and 87.5% white (Mutsaerts *et al.*, 2016).

280

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281 Duration of infertility, where reported, ranged from a mean of 19.5 months (Palomba *et al.*,  
282 2008) to 11 years (Aliyeva *et al.*, 1993). Some studies addressed women with any infertility  
283 history. Others centred on women undergoing fertility treatments or planning to start  
284 immediately following the intervention. Some were exclusively catered to persons with  
285 polycystic ovary syndrome (PCOS), with the syndrome defined by Rotterdam 2004 consensus  
286 criteria (ESHRE and Group, ASRM-Sponsored PCOS Consensus Workshop, 2004) in ten cases,  
287 National Institutes of Health (NIH) criteria (Zawadzki and Dunaif, 1992) in one case, ultrasound  
288 appearance of the ovaries in two cases, and not specified in five cases. One study used PCOS as  
289 an exclusion criterion (Moran *et al.*, 2003).

290

291 In eight studies, patients were anovulatory, and in seven studies patients had irregular  
292 menstrual cycles. Three papers were centred on patients who were resistant to clomiphene  
293 citrate for ovulation induction.

294

295 The lowest mean BMI was 24.5 kg/m<sup>2</sup> (Chavarro *et al.*, 2012), and the highest was 44 kg/m<sup>2</sup>  
296 (Mahoney, 2014; Hakonsen *et al.*, 2011).

297

298 Two studies were centred on men. One had participants with sperm DNA fragmentation who  
299 were overweight or obese (Faure *et al.*, 2014), while the other examined obese men only  
300 (Hakonsen *et al.*, 2011). One study examined a weight loss intervention in couples (Homan *et*  
301 *al.*, 2012).

302

### 303 ***Description of interventions***

304

305 Table 1 provides brief details of the types of interventions tested. In general, interventions were  
306 poorly described, with insufficient detail to allow their replication. Where described, most  
307 reducing diets followed healthy eating principles by reducing fat and refined carbohydrate

308 intake. Where available, studies described calorie intakes ranging from 1000 to 2000kcal/d  
309 (depending on body size), apart from three studies that tested very low calorie diets as part of  
310 their reducing diets (Tsagereli 2006, Kiddy 1992, van Dam 2004) and one that tested a very low  
311 carbohydrate ketogenic diet (Mavroupolos 2005). If physical activity advice or programmes  
312 were incorporated into interventions, they were generally for aerobic exercise. There was no  
313 clear evidence that any particular regime was more effective for weight loss, providing there  
314 was a weight reduction diet prescribed.

315  
316 Five of the 16 interventions incorporating both a dietary and physical activity component  
317 provided some part of the intervention in a group setting. Only two interventions were  
318 described involving couples. One study (Chavarro *et al.*, 2012) tracked participants' weights  
319 after administering a lifestyle questionnaire. While this is not strictly a weight-loss intervention,  
320 we have included it with the other cohort studies, because there is evidence that weight loss  
321 occurs with enrolment in studies tracking weight, even with minimal intervention (Waters *et al.*,  
322 2012; Johns *et al.*, 2016).

323

324

### 325 **Quality of studies**

326

327 The quality of the studies included was variable. For full details of risk of bias assessment for ~~all~~  
328 the randomised studies please see Supplementary Table SII. ~~The quality of the studies included~~  
329 ~~was variable.~~ Three of fourteen RCTs had four or five out of seven domains with low risk of bias,  
330 e.g. allocation concealment, incomplete outcome data, but the Lifestyle trial (Mutsaerts *et al.*,  
331 2016) stood out as the one with best quality. All studies were of high risk of bias with respect to  
332 blinding of participants to treatment allocation, and all had low risk of bias in at least two  
333 domains. Five of 26 non-randomised studies, having eight to nine of 14 domains with low risk of

334 bias, were judged to be good quality. [Full details of the risk of bias assessment for the non-](#)  
335 [randomised studies are given in Supplementary Table SIII.](#)

336

### 337 ***Studies involving female infertility participants***

338

#### 339 *Pregnancy*

340 Aggregated data from six RCTs show that women who received a combination of a reducing diet

341 and exercise had higher pregnancy rates than those who underwent standard **care** **(AUTHOR: is**  
342 **there a word missing? Please would you recheck the sense here? Thank you.)**, 238/434 (54.8%)

343 versus 221/443 (49.9%); RR 1.59, 95% CI (1.01, 2.50) (Figure 2). The trial by Mutsaerts *et al*

344 (2016) ) contributed significantly to the heterogeneity,  $I^2=71%$  and its exclusion in a post-hoc

345 sensitivity analysis reduced  $I^2$  to 0%. Although the numbers of participants in other RCTs were

346 too few for any meaningful conclusions to be drawn, a very small trial was unable to

347 demonstrate any advantage of diet alone, while another suggested that orlistat might be

348 beneficial. The results of an NRCT (Clark *et al*, 1998) support the result of the meta-analysis

349 favouring diet and exercise. The study by Koning *et al* (2015) did not show any advantage

350 associated with motivational interviewing.

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351 Table 2 details the reproductive outcomes for all included studies. Diet and exercise studies  
352 without control populations achieved rates that were comparable to those included in the meta-  
353 analysis.

354

#### 355 *Live births*

356 Data from five RCTs (Figure 3) did not favour diet and exercise over standard care in terms of  
357 live birth rates which were 48.9% (195/399) versus 46.8% (190/406) respectively; RR 1.54,  
358 95% CI (0.93, 2.56). Mutsaerts et al (Mutsaerts *et al.*, 2016) again contributed significantly to  
359 the heterogeneity,  $I^2=69\%$ . Its exclusion in a post-hoc sensitivity analysis reduced  $I^2$  to 0%, and  
360 resulted in diet and exercise having a statistical advantage, RR 1.86, 95% CI (1.25, 2.77). The  
361 NRCT (Clark *et al.*, 1995; Clark *et al.*, 1998) also favoured the intervention arm, 45/67 (67.2%)  
362 versus no treatment (0/20); RR 28.10, 95% CI (1.81, 436.85). Motivational interviewing was  
363 also not associated with an increased live birth rate.

364

365 Table 2 details live birth rates for all included studies. Women in studies on diet and exercise  
366 without control groups had lower success rates than those included in the meta-analysis.  
367 Khaskheli et al (Khaskheli *et al.*, 2013), who did not provide details of their intervention,  
368 reported a 37.6% (32/85) livebirth rate, while Crosignani et al, (Crosignani *et al.*, 2003), who  
369 administered a 1200 kcal/day diet along with aerobic exercise, achieved a 24.2% (8/33) rate.  
370 The numbers of participants in the other studies included in Table 2 were too few for any  
371 meaningful conclusions to be drawn.

372 *Spontaneous and IVF conceptions*

373 Pooled data from RCTs (Figures 4 and 5) show that, reducing diets and exercise were not  
374 associated with a higher chance of spontaneous conception [28.3% (86/304) versus 15.9%  
375 (50/315); RR 2.20, 95% CI (0.98, 4.93)].

376

377 *Miscarriages*

378 A combination of a reducing diet and exercise was associated with a pooled miscarriage rate of  
379 13.4 per hundred women (48/357) or 23.3% of pregnancies (48/206) (Figures 6 and 7). The  
380 control arm had a pooled miscarriage rate of 8.7 per hundred women (31/355) or 15.6% of  
381 pregnancies (31/199). This shows no benefit of diet and exercise [combined RR 0.96, 95% CI  
382 (0.89, 1.04) per woman and RR 0.91, 95% CI (0.91, 0.82, 1.01) per pregnancy]. Miscarriage rates  
383 in the other studies on diet and exercise vary widely (Table 2).

384

385 *Ovulation*

386 One RCT (Palomba *et al.*, 2010) found a 37.5% (12/32) ovulation improvement with a  
387 combination of reducing diet and exercise, while its control group had a 9.3% (3/32)  
388 improvement rate; RR 4.00 95% CI (1.25, 12.84) (Figure 8). An NRCT, also using diet and  
389 exercise, ~~that~~ had the highest rate of improvement of all included studies in its intervention  
390 group. [AUTHOR: again, does this sentence read correctly? Please would you recheck?], 89.6%  
391 (60/67), while none of the participants in the control group saw improvement; RR 37.37, 95%  
392 CI (2.41, 578.65).

393

394 One RCT (Kumar and Arora, 2014) compared the use of 120mg of orlistat twice daily and a  
395 lifestyle modification programme with use of the lifestyle programme alone. The orlistat group  
396 had a 50% (15/30) rate of ovulation, while the control group had a 6.7% (2/30) rate; RR 7.50,  
397 95% CI (1.88, 29.99).

398

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399 One RCT (Legro *et al.*, 2015) compared the proportions of total clomiphene treatment cycles  
400 that were ovulatory in each group. The group whose treatment was preceded by diet and  
401 exercise advice and the oral contraceptive pill (OCP) had the best ovulation rate, 67.1% (94/140),  
402 while the lifestyle alone group and control (OCP alone) group had rates of 60.3% (82/136) and  
403 46.1% (71/154) respectively.

404

405 Another RCT (Thomson *et al.*, 2008) randomised its participants, who had PCOS, to receive an  
406 energy-restricted high-protein diet alone (DO), combined with aerobic exercise (DA), or  
407 combined with both aerobic and resistance exercise (DC). DO saw a 50% (6/12) improvement  
408 in ovulation, DA a 50% (3/6) improvement, and DC a 42.8% (3/7) improvement.

409

410 Table 2 shows the ovulation rates in cohort studies of diet without controls. One study using a  
411 very low calorie diet (van Dam *et al.*, 2004) had a relatively good ovulation improvement rate,  
412 60% (9/15). Other studies had comparatively low rates, including one using a hypocaloric 1434  
413 kcal/day diet (Thomson *et al.*, 2009) which achieved a 19.2% (10/52) rate, and another  
414 (Turner-McGrievy *et al.*, 2014) which saw no improvement using either a low-calorie diet  
415 [LCD] (**AUTHOR: please define LCD**) or a vegan diet. One study compared a hypocaloric high  
416 protein diet to structured exercise training (SET) (Palomba *et al.*, 2008), and achieved a 25%  
417 (5/20) improvement rate with diet, and a 65% (13/20) improvement with exercise.

418

419 A study comparing ovulation improvement in women receiving acupuncture to those receiving  
420 an unspecified diet (Aliyeva *et al.*, 1993) had a 55% (11/20) improvement with the former, and  
421 46.7% (28/60) improvement in the latter; RR 1.18, 95% CI (0.73, 1.90).

422

#### 423 *Menstrual irregularity*

424 In clomiphene citrate resistant PCOS women, a single trial (Palomba *et al.*, 2010), showed that  
425 hypocaloric diet and exercise was significantly more likely to result in menstrual improvement,

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426 than observation only: 34.4% (11/32) versus 9.3% (3/32); RR 3.67, 95% CI (1.13, 11.92)  
427 (Figure 9). Other studies without control groups also suggest that diet and exercise were  
428 associated with improvement in menstrual regularity (Table 2). There were no RCTs evaluating  
429 the role of dietary interventions alone or motivational interviewing in regulating menstrual  
430 cyclicity. Data from observational and often uncontrolled studies of other interventions show  
431 variable levels of success (Table 2).

432

#### 433 *Oocyte retrieval*

434 Data from a single RCT (Figure 10) suggest that a low glycaemic index diet (Becker *et al.*, 2015)  
435 could improve oocyte yield in IVF. The mean (SD) number of oocytes in women in the  
436 intervention arm was 7.75 (5.39), compared to 4.18 (SD 3.01) in controls; mean difference -  
437 3.57, 95% CI (-6.87, -0.27).

438

#### 439 *Time to conception*

440 The Lifestyle trial (Mutsaerts *et al.*, 2016) reported that the median time to conception (TTC)  
441 resulting in a term live birth was 7.2 months (interquartile range (IQR) 2.6, 12.0) in the  
442 intervention group, who underwent a multidisciplinary programme based on diet and exercise,  
443 versus 5.2 (IQR 2.4, 10.1) in the control group, who were allowed fertility treatment from the  
444 start (P=0.06). An RCT comparing energy-restricted low protein and high protein diet groups  
445 who both received exercise instruction (Moran *et al.*, 2003) reported a 4-5 week TTC regardless  
446 of group. A cohort study which advised women to lose 10% of their body weight (Kort *et al.*,  
447 2013; Kort *et al.*, 2014) found that those who met the target had a mean TTC of 227 days, while  
448 those who had not had a mean of 231 days.

449

#### 450 *Weight loss*

451 Aggregated data from RCTs suggest that a combination of a reducing diet and exercise resulted  
452 in greater weight loss than that achieved in control groups (Figure 11); mean difference -3.98 kg

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453 (95% CI -4.85, -3.12). Diet alone was also shown to be more effective in a small RCT; mean  
454 difference -5.23kg (95% CI -7.42, -3.04) (Becker *et al.*, 2015).

455

456 In non-randomised trials, Clark et al (Clark *et al.*, 1998) reported significantly greater weight  
457 loss from diet and exercise; mean difference -9.00kg (95% CI -10.88, -7.12). Two non-  
458 randomised trials testing motivational interviewing also found greater weight loss; mean  
459 difference -3.21kg (95% CI -5.93, -0.49kg). Changes in weight, BMI and waist circumference for  
460 other studies are provided in Table 3. Generally results are not inconsistent with studies with  
461 either randomised or non-randomised control groups.

462

### 463 ***Comparisons with metformin***

464

#### 465 *Pregnancy*

466 Three small RCTs evaluated lifestyle interventions versus metformin (Figure 12). None was able  
467 to show any superiority of metformin over the alternative intervention, but it is difficult to be  
468 confident about these outcomes owing to the small sample sizes involved.

469

#### 470 *Ovulation*

471 Two small RCT of diet or drug treatment (Figure 13) were unable to show any benefit over  
472 metformin. Details of other studies are in Table 2.

473

#### 474 *Menstrual irregularity*

475 Metformin did not appear to improve menstrual regularity in a number of small trials  
476 comparing it to diet and exercise with or without drug treatment, diet alone or acarbose (Figure  
477 14). Details of other studies are in Table 2.

478

#### 479 *Weight loss*

480 Weight, BMI and waist circumference changes for studies comparing metformin with lifestyle  
481 interventions are provided in Table 3.

482 **AUTHOR: please would you mention Supplementary Table SIII (Quality assessment for non-**  
483 **randomised studies) at the appropriate place in the Results section? (Please renumber the**  
484 **Supplementary Tables if order in text requires it.) Thank you.**

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#### 485 **Summary of the key findings in infertile women**

486  
487 In overweight and obese infertile women, weight loss is associated with improved chances of  
488 becoming pregnant, and possibly spontaneous conception pre-IVF. Ovulation and menstrual  
489 irregularity are also aided. There appears to be no significant difference between weight loss  
490 interventions and controls with respect to rates of miscarriage and IVF conceptions. The few  
491 studies that included metformin showed no significant difference between weight loss  
492 interventions and the drug for achieving pregnancy or improvement in ovulation status;  
493 similarly there was no difference between the two groups in menstrual improvement.

#### 495 **Barriers to weight loss in infertile women**

496  
497 Very little has been reported regarding the perceived barriers to weight loss in overweight and  
498 obese infertile women. Two of the included studies attempted in some way to evaluate these.  
499 In the trial by Thomson et al (Thomson *et al.*, 2008), 104 participants were allocated to receive  
500 an energy restricted diet only (DO), the same diet combined with five sessions of aerobic  
501 walking and jogging exercise per week (DA), or the diet combined with aerobic and resistance  
502 training exercises (DC), where resistance exercise replaced two of the aerobic sessions (110)

503 **(AUTHOR: please would you use the correct format for the citation? Thank you.)** Forty-three of  
504 the participants in the trial (DO=13, DA=11 and DC=19) completed a validated Exercise  
505 Benefits/Barriers Scale at weeks 0, 10 and 20 (Thomson *et al.*, 2016). This was to determine  
506 their perceptions of the benefits and barriers to participation in exercise. The scale included 43

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507 items with statements related to ideas about exercise and a four-point Likert scale, with 4 =  
508 strongly agree, 3 = agree, 2 = disagree and 1 = strongly disagree. At baseline, the statements  
509 with the highest agreement were: “exercise tires me” [mean (SD), 2.86 (0.71)]; “exercise is hard  
510 work for me [2.79 (0.67)], and “I am fatigued by exercise” [2.60 (0.62)]. Those with the lowest  
511 agreement were: “my family members do not encourage me to exercise” [1.56 (0.59)], “my  
512 spouse does not encourage exercising” [1.63 (0.70)], and “I think people in exercise clothes look  
513 funny” [1.72 (0.59)].

514  
515 Barrier scores were reduced by week 10 in this study, regardless of treatment allocation, with  
516 no further reduction by week 20 ( $P \leq 0.001$ ). Time expenditure and physical exertion as  
517 perceived barriers saw a significant reduction ( $P \leq 0.003$ ), while family discouragement saw no  
518 change ( $P = 0.6$ ).

519  
520 Participants in the study by Galletly et al (Galletly *et al.*, 1996), in addition to completing a 24-  
521 week programme with weekly meetings comprising 1 hour of exercise and 1 hour of dietary and  
522 psychiatric counselling, completed the Rosenberg Self-Esteem Scale and the General Hospital  
523 Anxiety and Depression Scale at the start and end of the study. At baseline, those who dropped  
524 out before the end of intervention exhibited higher anxiety ( $p < 0.02$ ) and depression scores  
525 ( $p < 0.069$ ), and lower self-esteem scores ( $p < 0.056$ ) than those who completed. Completion was  
526 associated with a significant improvement in self-esteem ( $p < 0.0001$ ) and depression ( $p < 0.006$ ),  
527 and a non-significant reduction in anxiety scores.

528  
529 Based on what little evidence is available, overweight infertile women appear most deterred  
530 from exercise by the perception that it causes fatigue and is hard work. These perceptions, as  
531 well as depression, seem to decrease with continuation of an exercise programme. Very few  
532 women seem to be discouraged from exercise by family members. Those women who  
533 discontinue exercise would appear to be more anxious and/or depressed at the outset.

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**Studies involving male infertility participants**

*Achievement of pregnancy, live birth rate, and Improvement in sperm DNA integrity*

One cohort study (Faure *et al.*, 2014) administered a nutritionist-led personalised dietary programme of an unreported nature coupled with exercise, aimed at reducing intra-abdominal fat over a 3-8 month period, to eight men who had significant abdominal fat and at least 25% sperm DNA fragmentation and unexplained infertility (Table 4). The partners of all eight achieved pregnancy, three naturally and five through IUI, and all went on to have live births. Six who allowed their semen samples to be analysed both before and after the intervention all had an improvement in the degree of sperm DNA fragmentation.

**AUTHOR: could the following sections be edited to avoid repeating most of the data that are shown in Table 4, as we try to minimise such repetition in the results section? Thank you,**

*Improvement in semen analysis parameters*

A cohort of 44 men with BMI 33-61 kg/m<sup>2</sup> underwent a programme based on a healthy diet and daily exercise (Hakonsen *et al.*, 2011). Semen analyses before and afterward were compared in 27 men, and the results were as shown in Table 4.

The group with 3.5-12.1% weight loss (Group 1, n=9) saw a mean change in sperm concentration of -11 million/ml (95% CI -49, +27). The group with 12.2-17.1% (Group 2, n=9) loss had a mean change of +19 million/ml (95% CI -23, 61). The group with 17.2-25.4% loss (Group 3, n=9) had a mean change of +17 million/ml (95% CI -24, 58).

Group 1 saw a mean change in progressive sperm motility of -2%, 95% CI (-15,11). Group 2 had a mean change +4%, 95% CI (-10, 18). Group 3 had a mean change +11%, 95% CI (-3, 25).

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561 ~~Group 1 saw a mean change in normal sperm morphology of 0%, 95% CI (-2, 4). Group 2 had a~~  
562 ~~mean change of +1%, 95% CI (-3, 4). Group 3 had a mean change of +4%, 95% CI (1,7).~~

563

#### 564 *Change in weight*

565 ~~The cohort study by Hakonsen et al (Hakonsen et al., 2011) achieved median weight change~~  
566 ~~22kg, range -4 to 39 kg. The cohort study by Faure et al (Faure et al., 2014) achieved a mean~~  
567 ~~weight reduction of 4.40 (SD 5.0 kg). Table 4 also summarises the weight loss achieved in both~~  
568 ~~studies.~~

569

#### 570 *Summary*

571 The relative paucity of studies in overweight and obese men seeking fertility has made it  
572 difficult to draw firm conclusions regarding the benefits of weight loss. However, improvements  
573 in sperm concentrations, motility and normal morphology have been suggested, though these  
574 have not been statistically significant. Improvement in sperm DNA integrity has also been  
575 suggested, and this might be linked to an improved live birth rate.

576

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577 **Discussion**

578

579 ***Key findings***

580

581 The present systematic review and meta-analysis found that the weight loss interventions,  
582 particularly diet and exercise, improved pregnancy rates and ovulatory status. A trend toward  
583 more natural pregnancies, but not IVF pregnancies, occurred. Miscarriage rates were unaffected  
584 by weight loss interventions and, as reports of higher oocyte yield and improved menstrual  
585 regularity are based on single trials, further research is needed before firm conclusions can be  
586 made. A lack of RCTs in men and couples, and of studies evaluating barriers to undertaking  
587 weight loss in overweight and obese infertile populations, is evident. The quality of the studies  
588 we included was variable, but the one with the lowest risk of bias was the Lifestyle trial  
589 (Mutsaerts *et al.*, 2016), whose intervention also ranked highly for both pregnancy and live  
590 birth rates.

591

592 ***Women***

593

594 ***Pregnancies and live births***

595 Weight loss interventions, particularly those with reducing diets and exercise, were more likely  
596 than controls to result in pregnancy. Live births were reported by ~~only a few~~ relatively fewer  
597 studies. **[AUTHOR: correct?]**, usually involving women undergoing fertility treatments such as  
598 OI or IVF. Data from studies predating the Lifestyle trial in 2016 (Mutsaerts *et al.*, 2016)  
599 suggested that diet and exercise combinations were superior to standard care, but inclusion of  
600 this trial changed this. Those in the intervention arm underwent a 6-month programme based  
601 on diet and exercise, prior to undergoing 18 months of fertility treatments. Those in the control  
602 arm commenced fertility treatments immediately. The primary outcome was vaginal birth of a  
603 healthy singleton of at least 37 weeks' gestation within 24 months after randomisation. The trial

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604 was well conducted, with low risk of bias. This was the largest study in the review, and it carried  
605 substantial weight during meta-analysis. The results deviated from the trend exhibited by the  
606 preceding trials, resulting in marked increase in heterogeneity. It is possible that the results  
607 might have been different if the control group underwent 6 months of no intervention  
608 observation prior to 18 months of treatment. The trial found that significantly more women in  
609 the intervention group had ongoing pregnancies from natural (AUTHOR: the term natural' is  
610 usually preferred throughout but I leave the final decision to you.) conception than the control  
611 group, consistent with our other findings.

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612  
613 Studies reporting the highest pregnancy and live birth rates were not necessarily those with  
614 highest weight loss. Clark et al, had a high live birth rate of 67.2% in the diet and exercise arm of  
615 their NRCT, while also achieving one of the highest weight changes, mean -10.2kg (SD 4.3)  
616 (Clark *et al.*, 1995; Clark *et al.*, 1998). On the other hand, the intervention arm of the Mutsaerts  
617 et al (2016) RCT reported a live birth rate of 53.2%, but only achieved a mean weight change of  
618 -4.4 kg (SD 5.8).

619  
620 *Miscarriages*

621 Studies with some of the lowest rates of weight loss reported fewer miscarriages in their  
622 intervention arms, but the data are insufficient to draw conclusions (Tables 2 and 3).

623  
624 *Ovulation*

625 Weight loss interventions, regardless of their nature, were significantly more likely than control  
626 interventions to achieve ovulation in anovulatory women. Improvements were not necessarily  
627 greatest in those studies achieving the greatest weight loss.

628

629 *Menstrual irregularity*

630 A single RCT suggested that diet and exercise were significantly more likely to improve  
631 menstrual cycles than a control intervention (Palomba *et al.*, 2010). High rates of menstrual  
632 improvement were seen in studies with good weight or BMI reduction. Qublan et al (2007), for  
633 example, with a 1200-1400 kcal diet in their RCT, had a 61.9% menstrual improvement and  
634 achieved one of the better BMI reductions, with a mean change of -4.8 kg/m<sup>2</sup>.

635

636 *Spontaneous and IVF conceptions*

637 Studies included women expected to proceed to in-vitro treatments after a period of weight  
638 loss. Many women were able to conceive without further assistance through weight loss alone.  
639 All interventions showed an improved rate of spontaneous conception in comparison to a  
640 control. There was however no significant difference between interventions and controls when  
641 it came to IVF conceptions. Similar spontaneous conception rates were seen regardless of type  
642 of intervention and/or amount of weight lost.

643

644 *Change in weight, BMI and waist circumference*

645 No class of intervention was consistently better in achieving reduction in weight compared to  
646 others. Trials with longer interventions and follow-up sometimes suffered from higher rates of  
647 study drop-out, for example 20.4% in the 12-month Sim et al RCT (Sim *et al.*, 2014a) and 10.6%  
648 in the 6-month Mutsaerts et al RCT (Mutsaerts *et al.*, 2016), both of which mainly had diet and  
649 exercise. Others had no dropout: Karlsen et al after 7-8 months (Karlsen *et al.*, 2013) and  
650 Koning et al after 6 months (Koning, 2015), and both included motivational interviewing. This  
651 suggests that enhancing motivation plays a key role in compliance. Programmes with strict  
652 dietary and exercise modifications may be more likely to see discontinuation. The study with  
653 the most weight lost, the cohort study by Mavropoulos et al (Mavropoulos *et al.*, 2005), utilised

654 a very restrictive diet for 6 months, and had very low recruitment (n=11) and a high rate of  
655 drop-out (58.5%).

656

#### 657 *Metformin*

658 The meta-analyses showed that weight loss interventions have a non-significant advantage over  
659 metformin with respect to achievement of pregnancy or improvement of ovulation status. There  
660 was also no significant difference in menstrual regularity improvement. In light of these  
661 findings, and the gastro-intestinal side-effects common with metformin (Kumar and Arora,  
662 2014; Qublan *et al.*, 2007), lifestyle interventions should remain the first line therapy for  
663 improvement in ovulation and menstruation.

664

#### 665 *Interventions in infertile men*

666

667 There was very little evidence available to judge the effectiveness of weight reduction strategies  
668 in men, and this is an area ripe for future research. The two studies both utilised a diet and  
669 exercise combination, with neither providing adequate details of the intervention.

670

#### 671 *Types of diet*

672

673 As expected, the dietary interventions used were based on caloric restriction, and were usually  
674 consistent with weight reduction advice from national guidelines (National Clinical Guideline  
675 Centre, 2014; Dietz *et al.*, 2015). It is hard to say, based on the data obtained, whether any  
676 particular degree of restriction was superior for achievement of weight loss, particularly given  
677 the frequent pairing of diet with exercise. Some of the RCTs used individualized diets, tailoring  
678 caloric deficit to baseline weight (Becker *et al.*, 2015; Duval *et al.*, 2015b). Others mentioned a  
679 hypocaloric range within which dietary intakes would fall (Kumar and Arora, 2014; Qublan *et*  
680 *al.*, 2007; Thomson *et al.*, 2008; Turner-McGrievy *et al.*, 2014), generally between 1200 and

681 1800 kcal/day. Dieticians were used to assist with dietary advice in a few cases (Duval *et al.*,  
682 2015b; Turner-McGrievy *et al.*, 2014; Thomson *et al.*, 2008; Mutsaerts *et al.*, 2016). The RCT  
683 with the lowest recruitment and highest discontinuation rate used a vegan diet in one of its  
684 study arms (Turner-McGrievy *et al.*, 2014), suggesting poor acceptance.

685

### 686 ***Types of exercise***

687

688 The majority of exercise interventions sought to increase weekly aerobic activity in participants  
689 in order to increase caloric expenditure. The most frequent feature seen in the RCTs was an  
690 increase in the number of steps or amount of walking by participants (Duval *et al.*, 2015b;  
691 Karimzadeh and Javedani, 2010; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016; Sim *et al.*, 2014a;  
692 Thomson *et al.*, 2008). Fewer RCTs (**AUTHOR: correct, or studies?**) included strength or  
693 resistance training (Karimzadeh and Javedani, 2010; Moran *et al.*, 2011b; Thomson *et al.*, 2008),  
694 and this was always in addition to the basic aerobic approach. Thomson et al found that  
695 addition of resistance training did not result in a significantly different weight loss in their RCT  
696 of diet alone, diet with aerobic exercise, or diet with aerobic and resistance exercise (Thomson  
697 *et al.*, 2008). Physical activity interventions were in some cases individualised (Duval *et al.*,  
698 2015a; Moran *et al.*, 2011a) and in others in the form of group sessions (Moran *et al.*, 2003),  
699 with occasional use of a kinesiologist (Duval *et al.*, 2015a) or physiotherapist (Kumar and  
700 Arora, 2014).

701

### 702 ***Types of weight loss medication***

703

704 The use of weight loss drugs is contraindicated during pregnancy (Department of Veterans  
705 Affairs, 2014), and the studies using them aimed to reduce weight prior to attempting  
706 pregnancy. One trial (Legro *et al.*, 2015) recommended barrier contraception during its  
707 intervention. Oral medications used in the studies included orlistat, a lipase inhibitor;

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708 sibutramine, a selective serotonin and norepinephrine reuptake inhibitor; and acarbose, an  
709 alpha-glucosidase inhibitor shown to induce modest weight loss, though not suitable for weight  
710 maintenance (Hauner *et al.*, 2001). Of these, sibutramine, which has been withdrawn in Europe  
711 and the USA but is still available on the internet, has been shown in a large study to have a risk  
712 of cardiovascular defects in unborn infants (Källén, 2014), while the same study showed no risk  
713 of birth defects from orlistat use. The safety of acarbose in pregnancy is not established. Orlistat  
714 was shown to be superior to a control with respect to achievement of pregnancy and ovulation  
715 in a single study (Kumar and Arora, 2014). Until further evidence is available, lifestyle  
716 interventions should still be considered the first line therapy, with drug use reserved for  
717 monitored trials.

718

#### 719 ***Strengths and limitations of the review***

720

721 This review has added to the scope of the systematic review by Sim *et al.* (2014b) by going  
722 beyond examining overweight and obese women undergoing fertility treatment to encompass  
723 individuals of both genders, and couples, from a variety of infertility circumstances undergoing  
724 non-surgical weight loss programmes. A wide search strategy meant that we were thus able to  
725 capture 40 studies, in comparison to the 11 in that review (Sim *et al.*, 2014b). Author contact,  
726 initiated with 17 study authors, was another strength, as this allowed unreported information  
727 to be gained, and clarification of unclear information. Nevertheless, we cannot exclude  
728 publication bias, where studies with less positive outcomes remain unreported.

729

#### 730 ***Clinical recommendations***

731

732 Overweight and obese persons seeking fertility should be educated on the effects of being  
733 overweight or obese on the ability to achieve pregnancy, and the benefits of weight reduction,  
734 including improvement in pregnancy rates, and a reduced need for OI and IVF.

735  
736 A combination of a reduced calorie diet, which is not overly restrictive, and aerobic exercise,  
737 intensified gradually, should form the basis of programmes designed for such individuals. As  
738 compliance is key to success, coached sessions of achievable frequency, e.g. weekly, for up to 6  
739 months, should be considered. Motivational interviewing techniques might also be useful. An  
740 advantage of fertility care is that couples are catered to, and dual enrolment may result in better  
741 adherence, as partners tend to motivate each other.

742

#### 743 **Research recommendations**

744

745 Future research would ideally be in the form of large multi-centre RCTs including both women  
746 and men, ideally couples, attending fertility clinics and having at least one partner with a BMI  
747 within the overweight or obese range. Based on the data from RCTs of diet and exercise  
748 examined here, we estimate that a trial would require over 454 participants to detect a  
749 difference of 15% in pregnancy rates (90% power,  $p < 0.05$ , control pregnancy rate 50%,  
750 intervention rate 65%). This figure does not take account of losses to follow-up, and would need  
751 to be considerably inflated, depending on drop-out rates in feasibility and pilot work.

752

753 A reasonable control intervention would be the administration of dietary and exercise advice  
754 only-, to be undertaken for a brief period ~~only~~ (AUTHOR: correct?), to reduce persons allocated  
755 to this arm feeling as though their fertility treatments were being delayed with no intervention.  
756 Similar durations employed between intervention and control groups prior to starting fertility  
757 treatments would allow for fair comparisons with respect to weight loss and reproductive  
758 outcomes.

759

760 A long duration of follow-up, spanning decades, might answer further questions, including  
761 whether obstetric problems related to weight such as gestational diabetes or caesarean rates

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762 might be reduced in imminent or future pregnancies. The permanency of lifestyle changes made  
763 while attempting fertility might also be established, as well as their impact on family members,  
764 and the maintenance of weight loss in the long term. ~~The role of epigenetic changes might also~~  
765 ~~be explored. (AUTHOR: although important, and you are discussing possible future research~~  
766 ~~here, this subject has not been mentioned so far and seems a little unrelated to the overall~~  
767 ~~approach here. It is also unclear what particular studies you would perform, therefore I suggest~~  
768 ~~removing it, which would not detract from the discussion. If you agree, please edit accordingly?~~  
769 ~~Thank you.)~~

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Commented [BDA18]: Removed reference to epigenetic studies.

## 771 **Conclusions**

772  
773 Non-surgical weight reduction strategies in the infertile have been shown to improve  
774 reproductive outcomes in both men and women. Diet, exercise, a combination of the two,  
775 weight-loss medication and motivational interviewing have all been efficacious in reducing  
776 obesity. In women, weight loss from diet and exercise is associated with improved chances of  
777 becoming pregnant, with a trend toward improved live birth rate. Ovulation and menstrual  
778 irregularity are also aided. At present there appears to be no significant difference between  
779 weight loss interventions and control interventions with respect to rates of miscarriage and IVF  
780 conceptions. Well-designed RCTs should also shed light on the effect of weight loss on numbers  
781 of oocytes retrieved and other parameters in IVF cycles, and on TTC, as well as the role of  
782 interventions in couples. In men, improvements in sperm concentrations, motility and normal  
783 morphology have been suggested, as well as in sperm DNA integrity, but further high quality  
784 research is needed to confirm these findings and demonstrate improvement in live birth rates in  
785 their partners.

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787 Mrs Cynthia Fraser provided useful assistance in the formulation of a search strategy. Authors  
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789 Sim, Amany Salama, Rebecca Thomson, Cherrie Galletly, and Hanno Pijl.

790 **Authors' roles**

791 Dr Damian Best was involved in design and conduct of the review, data analysis, drafting the  
792 manuscript and critical discussion. Professor Alison Avenell was involved in the design and  
793 conduct of the review, supervised data analysis, checked data extraction, and was involved in  
794 manuscript revision and critical discussion. Professor Siladitya Bhattacharya was involved in  
795 the design of the review and contributed to manuscript revision and critical discussion.

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800

801 **Conflict of interest**

802 None declared.

803

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1033 **Figure legends**

1034 **AUTHOR: I have files for a Figure 1 (PRISMA chart in tiff format) plus Figures 2-14 in eps**  
1035 **format. The legends below are for only 13 figures. Please would you recheck the figure**  
1036 **numbering/titles?**

1037 Figure 1. PRISMA flow diagram illustrating the process of selection of studies for inclusion in the  
1038 systematic review. **AUTHOR: please would you provide a higher quality image for Production?**

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1040 Figure 2. **AUTHOR: it may be helpful to also state in all titles that these are Forest plots.** Forest  
1041 plot - Pregnancies associated with diet, diet and exercise, orlistat and motivational interviewing  
1042 versus control.

1044 Figure 3. Forest plot - Intervention versus control: live births.

1045 Figure 4. Forest plot - Intervention versus control: spontaneous conceptions.

1046 Figure 5. Forest plot - Intervention versus control: IVF conceptions.

1047 Figure 6. Forest plot - Intervention versus control: miscarriages for all participants enrolled.

1048 Figure 7. Forest plot - Intervention versus control: miscarriages for women who became  
1049 pregnant.

1050 Figure 8. Forest plot - Intervention versus control: ovulation improvement.

1051 Figure 9. Forest plot - Intervention versus control: improvement of menstrual irregularity.

1052 Figure 10. Forest plot - Intervention versus control: oocytes retrieved per female participant.

1053 Figure 11. Forest plot - Intervention versus control: change in weight (kg).

1054 Figure 12. Forest plot - Intervention versus metformin: women who became pregnant.

1055 Figure 13. Forest plot - Intervention versus metformin: improvement in ovulation.

1056 Figure 14. Forest plot - Intervention versus metformin: improvement in menstrual irregularity  
1057 per irregular menstruating female participant

1059 **AUTHOR: we tend not to include Appendices, therefore these data have been**  
1060 **divided and renamed as supplementary files. The quality of the file for the**

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**AUTHOR:** for accuracy, please could you include *et al* in the references in the tables below, where required? Thank you.

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**Table 1. Types of interventions evaluated in studies of weight loss interventions and fertility in women and men who are overweight or obese.**

Reducing diet/healthy eating and exercise programme or advice	
<del>Duval</del> Duval <i>et al</i> 2015 G	RCT
<del>Karimzadeh</del> Karimzadeh <i>et al</i> 2010	RCT
<del>Moran</del> Moran <i>et al</i> 2011	RCT
<del>Mutsaerts</del> Mutsaerts <i>et al</i> 2016	RCT
<del>Palomba</del> Palomba <i>et al</i> 2010 G	RCT
<del>Sim</del> Sim <i>et al</i> 2014 G	RCT
<del>Clark</del> Clark <i>et al</i> 1998 G	Non-RCT
<del>Crosignani</del> Crosignani <i>et al</i> 2003	Cohort
De Frène 2015	Cohort
<del>Faure</del> Faure <i>et al</i> 2014	Cohort
<del>Galletly</del> Galletly <i>et al</i> 1996a G	Cohort
<del>Galletly</del> Galletly <i>et al</i> 1996b G	Cohort
<del>Hakonsen</del> Hakonsen <i>et al</i> 2011	Cohort
<del>Hollman</del> Hollman <i>et al</i> 1996	Cohort
<del>Khaskheli</del> Khaskheli <i>et al</i> 2013	Cohort
<del>Mahoney</del> Mahoney <i>et al</i> 2014	Cohort
<del>Miller</del> Miller <i>et al</i> 2008 G	Cohort
<del>Salama</del> Salama <i>et al</i> 2015	Cohort
Reducing diet/healthy eating, weight loss drugs, and exercise programme or advice	
<del>Legro</del> Legro <i>et al</i> 2015	RCT
<del>Lazurova</del> Lazurova <i>et al</i> 2004	Non-RCT
<del>Kort</del> Kort <i>et al</i> 2014	Cohort
Reducing diet/health eating, or type of diet	

<u>Becker</u> <u>Becker et al</u> 2015	RCT
<u>Moran</u> <u>Moran et al</u> 2003	RCT
<u>Qublan</u> <u>Qublan et al</u> 2007	RCT
<u>Turner-McGrievy</u> <u>Turner-McGrievy et al</u> 2014	RCT
<u>Aliyeva</u> <u>Aliyeva et al</u> 1993	Non-RCT
<u>Palomba</u> <u>Palomba et al</u> 2008 G	Non-RCT
<u>Awartani</u> <u>Awartani et al</u> 2012	Cohort
<u>Kiddy</u> <u>Kiddy et al</u> 1992	Cohort
<u>Mavropoulos</u> <u>Mavropoulos et al</u> 2005 G	Cohort
<u>Thomson</u> <u>Thomson et al</u> 2009	Cohort
<u>Tsagareli</u> <u>Tsagareli et al</u> 2006	Cohort
<u>Van Dam</u> <u>Van Dam et al</u> 2004	Cohort
<b>Behavioural therapy, including motivational interviewing</b>	
<u>Karlsen</u> <u>Karlsen et al</u> 2013	Non-RCT
<u>Koning</u> <u>Koning et al</u> 2015 C	Non-RCT
<u>Homan</u> <u>Homan et al</u> 2012	Cohort
<b>Exercise programme</b>	
<u>Thomson</u> <u>Thomson et al</u> 2008 G	RCT
<u>Palomba</u> <u>Palomba et al</u> 2008	Non-RCT
<b>Orlistat</b>	
<u>Kumar</u> <u>Kumar et al</u> 2014	RCT
<b>Metformin</b>	
<u>Karimzadeh</u> <u>Karimzadeh et al</u> 2010	RCT
<u>Kumar</u> <u>Kumar et al</u> 2014	RCT
<u>Qublan</u> <u>Qublan et al</u> 2007	RCT
<u>Sonmez</u> <u>Sonmez et al</u> 2005	RCT
<u>Lazurova</u> <u>Lazurova et al</u> 2004	Non-RCT
<b>Acarbose</b>	
<u>Sonmez</u> <u>Sonmez et al</u> 2005	RCT
<b>Detailed lifestyle questionnaire</b>	



Study ID	Intervention arm	Pregnancies per participant			% Live births per participant		% Miscarriages per participant (fewer = better)		% Miscarriages per pregnancy (fewer = better)		% Improved ovulation per anovulatory participant		% Improved menstrual irregularity / irregular menses per participant		Time to conception per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
<a href="#">Palomba</a> <a href="#">Palomba et al 2008</a>	Exercise	20	14	35.0			7	5.0	5	14.3	5	65.0				
<a href="#">Homan</a> <a href="#">Homan et al 2012</a>	Motivational interviewing	35	15	34.8			5	4.3	3	12.5						
<a href="#">Awartani</a> <a href="#">Awartani et al 2012</a>	Weight reduction advised	90	16	34.4												
<a href="#">Qublan</a> <a href="#">Qublan et al 2007</a>	Diet	24	17	33.3			4	4.2	3	12.5	10	50.0	11	61.9		
<a href="#">Legro</a> <a href="#">Legro et al 2015</a>	Diet & exercise	50	18	32.0	9	26.0	9	6.0	10	18.8	6	60.3				
<a href="#">Crosignani</a> <a href="#">Crosignani et al 2003</a>	Diet & exercise	33	19	30.3	10	24.2					8	55.6	6	66.7		
<a href="#">Aliyeva</a> <a href="#">Aliyeva et al 1993</a>	Diet	60	20	30.0							14	46.7	8	63.3		
<a href="#">Kiddy</a> <a href="#">Kiddy et al 1992</a>	Very low calorie diet/Low calorie diet	24	21	29.2	14	16.7	10	8.3	13	28.6			20	29.4		
<a href="#">Hollman</a> <a href="#">Hollman et al 1996</a>	Diet & exercise	35	22	28.6	12	22.9	8	5.7	11	20.0			3	80.0		
<a href="#">Legro</a> <a href="#">Legro et al 2015</a>	Diet, exercise, oral contraceptive pill	50	23	28.0	11	24.0	3	4.0	5	14.3	4	67.1				
<a href="#">Qublan</a> <a href="#">Qublan et al 2007</a>	Metformin	22	24	27.3			6	4.5	7	16.7	15	45.5	12	61.1		
<a href="#">Kumar</a> <a href="#">Kumar et al 2014</a>	Metformin	30	25	26.7							20	23.3				
<a href="#">Becker</a> <a href="#">Becker et al 2015</a>	Diet	14	26	21.4	13	21.4										
<a href="#">Karimzadeh</a> <a href="#">Karimzadeh et al 2010</a>	Diet & exercise	75	26	20.0									6	66.7		
<a href="#">Lazurova</a> <a href="#">Lazurova et al 2004</a>	Metformin	30	28	20.0									4	70.0		
<a href="#">Miller</a> <a href="#">Miller et al 2008</a>	Diet & exercise	12	29	16.7									1	83.3		
<a href="#">Karimzadeh</a> <a href="#">Karimzadeh et al 2010</a>	Metformin & clomiphene	88	30	14.8									10	62.5		
DeFrene 2015	Diet & exercise	23	31	13.0												
<a href="#">Karimzadeh</a> <a href="#">Karimzadeh et al 2010</a>	Metformin	90	32	12.2									13	55.6		
<a href="#">Salama</a> <a href="#">Salama et al 2015</a>	Mediterranean diet & exercise	58	33	12.1									9	62.8		

Study ID	Intervention arm	Pregnancies per participant			% Live births per participant		% Miscarriages per participant (fewer = better)		% Miscarriages per pregnancy (fewer = better)		% Improved ovulation per anovulatory participant		% Improved menstrual irregularity / irregular menses per participant		Time to conception per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
<del>Turner-McGrievy</del> Turner-McGrievy <i>et al</i> 2014	Low calorie diet	9	34	11.1							22	0.0				
<del>Palomba</del> Palomba <i>et al</i> 2008	Diet	20	35	10.0			1	0.0	1	0.0	19	25.0				
<del>Galletly</del> Galletly <i>et al</i> 1996(a)	Exercise & advice	96	36	9.4												
<del>Moran</del> Moran <i>et al</i> 2003	High protein diet	14	37	8.7									21	26.1	1	4-5 weeks
<del>Lazurova</del> Lazurova <i>et al</i> 2004	Sibutramine, diet, exercise	15	38	6.7									14	53.3		
<del>Thomson</del> Thomson <i>et al</i> 2008	Diet & aerobic exercise	31	39	6.3							10	50.0	17	42.9		
<del>Moran</del> Moran <i>et al</i> 2003	Low protein diet	14	40	4.3									22	22.7	1	4-5 weeks
<del>Thomson</del> Thomson <i>et al</i> 2008	Diet	30	41	3.3							10	50.0	24	21.4		
<del>Palomba</del> Palomba <i>et al</i> 2010	Diet & exercise, Clomiphene	32	42	3.1							18	37.5	19	34.4		
<del>Thomson</del> Thomson <i>et al</i> 2008	Diet & aerobic & resistance exercise	33	43	3.0							16	42.8	16	44.4		
Turner McGrievy 2014	Vegan diet	9	44	0							22	0.0				
<del>Sonmez</del> Sonmez <i>et al</i> 2005	Acarbose	15									2	86.7	5	69.2		
<del>Sonmez</del> Sonmez <i>et al</i> 2005	Metformin	15									3	80.0	2	80.0		
<del>Van Dam</del> Van Dam <i>et al</i> 2004	Very low calorie diet	15									6	60.0				
<del>Thomson</del> Thomson <i>et al</i> 2009	Diet	52									20	19.2	18	42.3		
<del>Palomba</del> Palomba <i>et al</i> 2010	Diet & exercise	32									21	12.5	25	12.5		
<del>Mahoney</del> Mahoney <i>et al</i> 2014	Motivational interviewing, diet, exercise												23	22.2		



**Table 3. Weight reduction outcomes for women (lower numbers for ranking indicate better outcomes).**

Study ID	Intervention Arm	Mean Weight change (kg) Per Participant			Mean BMI change (kg/m <sup>2</sup> ) Per Participant		Mean Waist Circumference change (cm) Per Participant	
		N	Rank	Change	Rank	Change	Rank	Change
<a href="#">Mavropoulos et al 2005</a>	Low calorie ketogenic diet	5	1	-12.34 ± 6.37	8	-4.0		
<a href="#">Hollman et al 1996</a>	Diet & exercise	35	2	-10.2 ± 7.9	10	-3.4 (median)		
<a href="#">Clark et al 1998</a>	Diet & exercise	67	3	-10.2 ± 4.3	9	-3.7 ± 1.6		
<a href="#">Thomson et al 2008</a>	Diet & aerobic exercise	31	4	-10.1 ± 5.6			1	-11.7 ± 6.1
<a href="#">Karlsen et al 2013</a>	Motivational interviewing	110	5	-9.3	11	-3.3		
<a href="#">Thomson et al 2009</a>	Diet	52	6	-9.0 ± 0.8 (SEM)			4	-10.4 ± 0.9 (SEM)
<a href="#">Thomson et al 2008</a>	Diet	30	7	-8.6 ± 6.0			3	-10.8 ± 7.1
<a href="#">Thomson et al 2008</a>	Diet & aerobic & resistance exercise	3	8	-8.6 ± 5.2			2	-11.0 ± 6.3
<a href="#">Moran et al 2003</a>	High protein diet	14	9	-8.5 ± 1.1				
<a href="#">Kumar et al 2014</a>	Orlistat	30	10	-7.81 ± 0.66%	4	-8.12 ± 6.71%		
<a href="#">Kumar et al 2014</a>	Metformin	30	11	-7.78 ± 0.57% (SEM)	3	-8.40 ± 0.65% (SEM)	14	-2.68 ± 0.16% (SEM)
<a href="#">Kiddy et al 1992</a>	Very low calorie diet/low calorie diet	24	12	-6.9 ± 6.7				
<a href="#">Moran et al 2003</a>	Low protein diet	14	13	-6.9 ± 0.8 (SEM)				
<a href="#">Sim et al 2014</a>	Diet & exercise	26	14	-6.6 ± 4.6	14	-2.4 ± 1.6	6	-8.7 ± 5.6
<a href="#">Salama et al 2015</a>	Mediterranean diet & exercise	58	15	-6.3 ± 20.8	16	-2.37 ± 7.28	7	-6.45 ± 14.13
<a href="#">Legro et al 2015</a>	Lifestyle	50	16	-6.2, 95% CI (-7.3, -5.3)			8	-6.3, 95% CI (-9.2, -3.4)
<a href="#">Galletly et al 1996(b)</a>	Diet and exercise	58	17	-6.2 ± 4.5	13	-2.4 ± 1.7		
<a href="#">Legro et al 2015</a>	Diet, exercise, oral contraceptive pill	50	18	-6.1, 95% CI (-7.0, -5.2)			9	-6.2, 95% CI (-9.1, -3.3)
<a href="#">Tsagareli et al 2006</a>	Very low calorie diet	6	19	-5.6; Range -8.2 to -5.3	17	-2.1; Range -1.8 to -3.2	5	-10.0; Range -7 to -14
<a href="#">Galletly et al 1996(a)</a>	Diet & exercise	96	20	-5.2 ± 5.1				
<a href="#">Becker et al 2015</a>	Diet	14	21	-4.51 ± 0.83 (SEM)			15	-1.31 ± 10.5
<a href="#">Palomba et al 2010</a>	Diet & exercise, Clomiphene	32	22	-4.42 ± 9.22	12	-2.64 ± 4.26	11	-4.92 ± 5.87

Study ID	Intervention Arm	N	Mean Weight change (kg) Per Participant		Mean BMI change (kg/m <sup>2</sup> ) Per Participant		Mean Waist Circumference change (cm) Per Participant	
			Rank	Change	Rank	Change	Rank	Change
<del>Mutsaerts</del> <a href="#">Mutsaerts et al 2016</a>	Diet & exercise	280	23	-4.4 ± 5.8	21	-1.3 (Median) IQR (-2.5, -0.07)		
<del>Koning</del> <a href="#">Koning et al 2015</a>	Motivational interviewing	102	24	-4.3 ± 0.8 (SEM)	20	-1.4 ± 0.3 (SEM)		
<del>Palomba</del> <a href="#">Palomba et al 2010</a>	Diet & exercise	32	25	-4.21 ± 8.56	15	-2.39 ± 3.54	12	-3.84 ± 6.35
<del>Moran</del> <a href="#">Moran et al 2011</a>	Diet & exercise	18	26	-3.8 ± 3.0	19	-1.4 ± 1.1	10	-5.3 ± 4.6
<del>Mahoney</del> <a href="#">Mahoney et al 2014</a>	Motivational interviewing, diet, exercise	9	27	-3.18 ± 2.27	24	-0.7 ± 7.31		
<del>Turner-McGrievy</del> <a href="#">Turner-McGrievy et al 2014</a>	Vegan diet	9	28	-2.1 ± 3.5				
<del>Turner-McGrievy</del> <a href="#">Turner-McGrievy et al 2014</a>	Low calorie diet	9	29	-0.4 ± 0.9				
<del>Chavarro</del> <a href="#">Chavarro et al 2012</a>	Questionnaire	170	30	&0.3 (Median) IQR (-0.1, 1.8)				
<del>Kort</del> <a href="#">Kort et al 2014</a>	Diet & exercise	52			1	-13.89% ± 3.71% in 17 with 10% weight loss -3.79% ± 3.98% in 35 with <10% weight loss		
<del>Khaskheli</del> <a href="#">Khaskheli et al 2013</a>	Diet & exercise	85			2	-9.6 ± 1.23		
<del>Lazurova</del> <a href="#">Lazurova et al 2004</a>	Sibutramine, diet, exercise	15			5	-4.6 ± 4.2 (SEM)		
<del>Qublan</del> <a href="#">Qublan et al 2007</a>	Diet	24			6	-4.8		
<del>Qublan</del> <a href="#">Qublan et al 2007</a>	Metformin	22			7	-4.1		
<del>Miller</del> <a href="#">Miller et al 2008</a>	Diet & exercise	12			18	-2.06 ± 0.51 (SEM)		
<del>Sonmez</del> <a href="#">Sonmez et al 2005</a>	Acarbose	15			22	-1.1 ± 2.78		
<del>Lazurova</del> <a href="#">Lazurova et al 2004</a>	Metformin	30			23	-0.85 ± 0.38 (SEM)		
<del>Sonmez</del> <a href="#">Sonmez et al 2005</a>	Metformin	15			25	-0.3 ± 2.47		
<del>Homan</del> <a href="#">Homan et al 2012</a>	Motivational interviewing	35		"47% of the overweight participants had a modest loss of between 1 and 5 kg (not statistically significant)"				-3.8 in ½ of those attending follow-up and not pregnant
<del>Duval</del> <a href="#">Duval et al 2015</a>	Diet & exercise	24		10/24 had ≥ 5% weight loss				12/24 had ≥ 5cm reduction (compared to 11/31 in control group)

Study ID	Intervention Arm	Mean Weight change (kg) Per Participant			Mean BMI change (kg/m <sup>2</sup> ) Per Participant		Mean Waist Circumference change (cm) Per Participant	
		N	Rank	Change (compared to 11/31 in control group)	Rank	Change	Rank	Change
<a href="#">Karimzadeh</a> <a href="#">Karimzadeh et al 2010</a>	Diet & exercise	75						Significantly lower waist circumference (P=0.001) in the lifestyle group than in the clomiphene, metformin, and clomiphene/metformin groups
<a href="#">Aliyeva</a> <a href="#">Aliyeva et al 1993</a>	Diet	60		“30-40% decrease in body weight in 2-4 months”				
<a href="#">Aliyeva</a> <a href="#">Aliyeva et al 1993</a>	Acupuncture	20		“Slower rate and extent of weight reduction: 7-9 months”				
<a href="#">Awartani</a> <a href="#">Awartani et al 2012</a>	Weight reduction advised	90				23/90 reduced their BMI below 35; 65/90 did not		
<a href="#">Crosignani</a> <a href="#">Crosignani et al 2003</a>	Diet & exercise	33						Those with 5% weight loss had mean waist circumference 94 cm, SD 9 Those with 10% weight loss had mean 86, SD 7
<a href="#">Van Dam</a> <a href="#">Van Dam et al 2004</a>	Very low calorie diet	15		14/15 loss at least 10% of body weight				
<a href="#">Palomba</a> <a href="#">Palomba et al 2008</a>	Exercise	20		Ovulatory (n=13): Mean -5.6%, SD 1.6% Anovulatory (n=7): Mean -2.0%, SD 0.2%		Ovulatory (n=13): Mean -10.0%, SD 3.7% Anovulatory (n=7): Mean -1.4%, SD 2.1%		Ovulatory (n=13): Mean -9.6%, SD 2.1% Anovulatory (n=7): Mean -2.5%, -SD 2.9%
<a href="#">Palomba</a> <a href="#">Palomba et al 2008</a>	Diet	20		Ovulatory (n=5): Mean -10.5%, SD 4.1% Anovulatory (n=15): Mean -2.3%, SD 3.1%		Ovulatory (n=5): Mean -15.4%, SD 3.9% Anovulatory (n = 15): Mean -4.0%, SD 5.2%		Ovulatory (n=5): Mean -9.4%, SD 2.5% Anovulatory (n=15): Mean -2.8%, SD 3.1%

**Table 4. Reproductive and weight outcomes for infertile men.**

	<del>Faure</del> <i>Faure et al</i> 2014 N=8	<del>Hakonsen</del> <i>Hakonsen et al</i> 2011 N=27 of 44 at follow-up
Clinical pregnancy rate	8/8	
Live birth rate	8/8	
Improvement in sperm DNA integrity	6/6 consenting to semen analysis upon completion	
Change in sperm concentration (million/ml)		Group 1 (n=9) Mean -11 95% CI -49, 27
Group 1: Weight loss 3.5-12.1%		Group 2 (n=9) Mean +19 95% CI -23, 61
Group 2: Weight loss 12.2-17.1%		Group 3 (n=9) Mean +17 95% CI -24, 58
Group 3: Weight loss 17.2-25.4%		
Change in sperm motility (% motile)		Group 1 (n=8) Mean -2 95% CI -15, 11
		Group 2 (n=9) Mean +4 95% CI -10, 18
		Group 3 (n=9) Mean +11 95% CI -3, 25
Change in normal sperm morphology (% normal forms)		Group 1 (n=9) Mean 0 95% CI -2, 4
		Group 2 (n=9) Mean +1 95% CI -3, 4
		Group 3 (n=9) Mean +4 95% CI 1, 7
Change in weight (kg)	Mean -4.40 SD 5.00	Median -22 Range -4 to -39
Change in BMI (kg/m <sup>2</sup> )	Mean -1.22 SD 1.38	
Change in Waist circumference (cm)	Mean -8.50 SD 7.89	