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

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

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

SEARCH METHODS: An electronic search of MEDLINE, EMBASE and the Cochrane Library was performed for studies between January 1966 and March 2016. Text word and MESH search terms used related to infertility, weight and barriers to weight loss. Inclusion criteria were an intervention to change lifestyle evaluated in any study design in participants of either gender with an unfulfilled desire to conceive. Studies were excluded if they included participants not attempting pregnancy, with illnesses that might cause weight fluctuations, or studies evaluating bariatric surgery. Two reviewers performed data extraction and quality assessment using the Cochrane Risk of Bias Tool for randomized trials, and a ratified checklist (ReBIP) for non-randomized studies.

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

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

Key words: infertility / obesity / weight loss / systematic review / diet / exercise

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Introduction

Overweight is defined by the World Health Organization (WHO) (World Health Organization, 2016) as a BMI ≥ 25 kg/m^2, and obesity as ≥ 30 kg/m^2. The prevalence of obesity is increasing worldwide (World Health Organization, 2016), with more than 600 million obese adults, including 15% of women, in 2014—double the prevalence reported three decades earlier. Infertility is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild et al., 2009; National Institute for Health and Clinical Excellence, 2013). Using this definition, infertility affects ~1 in 7 couples in the UK, which is similar to an estimate of prevalence in the USA (Thoma et al., 2013). An increasingly overweight and obese population has led to a greater proportion of individuals with high BMI being evaluated in infertility settings (Vahratian and Smith, 2009).

BMI has been associated with delayed conception in women in a dose-dependent fashion (Gesink Law et al., 2007; Wise et al., 2010, 2013). It is thought to produce anovulation (Zain and Norman, 2008; Klenov and Jungheim, 2014), which results in menstrual irregularity (Hartz et al., 1979; Zain and Norman, 2008); impairment of oocyte development (Klenov and Jungheim, 2014) and quality (Carrell et al., 2001; Metwally et al., 2007); and it also has direct effects on the endometrium (Bellver et al., 2011). With ovulation induction (OI) treatment, higher doses of medications (Dickey et al., 1997; Balen et al., 2006a) and a longer period of stimulation (Balen et al., 2006b) are required with a higher BMI. With IVF, the chances of achieving a pregnancy decrease with each unit increase in BMI (Ferlitsch et al., 2004), and it is thought that implantation rates are lower in obese women (Styne-Gross et al., 2005; Bellver et al., 2010). An increased risk of miscarriage following IVF has also been reported (Maheshwari et al., 2007).

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

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

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

Methods

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

Criteria for considering studies for this review

Types of studies

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

Types of participants

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

Types of interventions

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

Types of outcome measures

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

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

Search methods for identification of studies

The dates searched were 1 January 1966–19 March 2016. No restriction was placed on language of origin, and studies could be included regardless of whether they had been published. The electronic databases used were MEDLINE, EMBASE and the Cochrane Library. Additional studies were identified through review of the references of the retrieved papers, contact with study authors, and online searching of Google and Google Scholar (Google Inc., Mountain View, CA, USA). The search strategy used for MEDLINE and EMBASE is given in the Supplementary Data.

Data collection and analysis

Selection of studies

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

Data collection process

Data were extracted by one reviewer (D.B.), and checked by a second (A.A.). Discrepancies were resolved by discussion between the reviewers, and a third reviewer (S.B.) was available for referral as necessary. Study authors were contacted as required for missing data or clarification.

For each included study, the information collected included study design; methods; location, setting and time period; information about the participants (demographics, infertility diagnosis, BMI, eligibility criteria); drop-outs; the types of interventions assessed and their descriptions; and outcomes, including pregnancy, live births, weight or BMI change, miscarriage, ovulation and menstrual change. For men, semen analysis parameters were captured. Any data on barriers to weight loss were also captured. Data on costs and cost-effectiveness were sought but not found.

Assessment of risk of bias in individual studies

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

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

Summary measures

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

Synthesis of results

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

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unavoidable population and intervention heterogeneity, as anticipated in interventions for weight loss.

Assessment of heterogeneity

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

Sensitivity analyses

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

Results

Outcome of the search

Details of the selection process for studies is summarized in the PRISMA flow diagram (Fig. 1). Seventeen study authors were contacted for clarification or further information; ten provided helpful further information.

Full details of all the studies and interventions are provided in Supplementary Table SI. There were 14 RCTs, 6 non-randomized studies with comparison groups (NRCTs) and 20 cohort studies with interventions. Ten studies took place in Australia, seven in the USA, three each in Italy and the Netherlands, and two in Denmark. One each came from Belgium, Brazil, Canada, Egypt, France, Germany, India, Iran, Jordan, Pakistan, Russia, Saudi Arabia, Slovakia, Turkey and the UK. Three studies were multi-centre.

Enrolment varied from 8 participants (Faure et al., 2014) to 577 (Mutsaerts et al., 2016). Attrition rates ranged from 10.6% (Mutsaerts et al., 2016) to 66.7% (Turner-McGrievy et al., 2014).

Description of populations

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

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

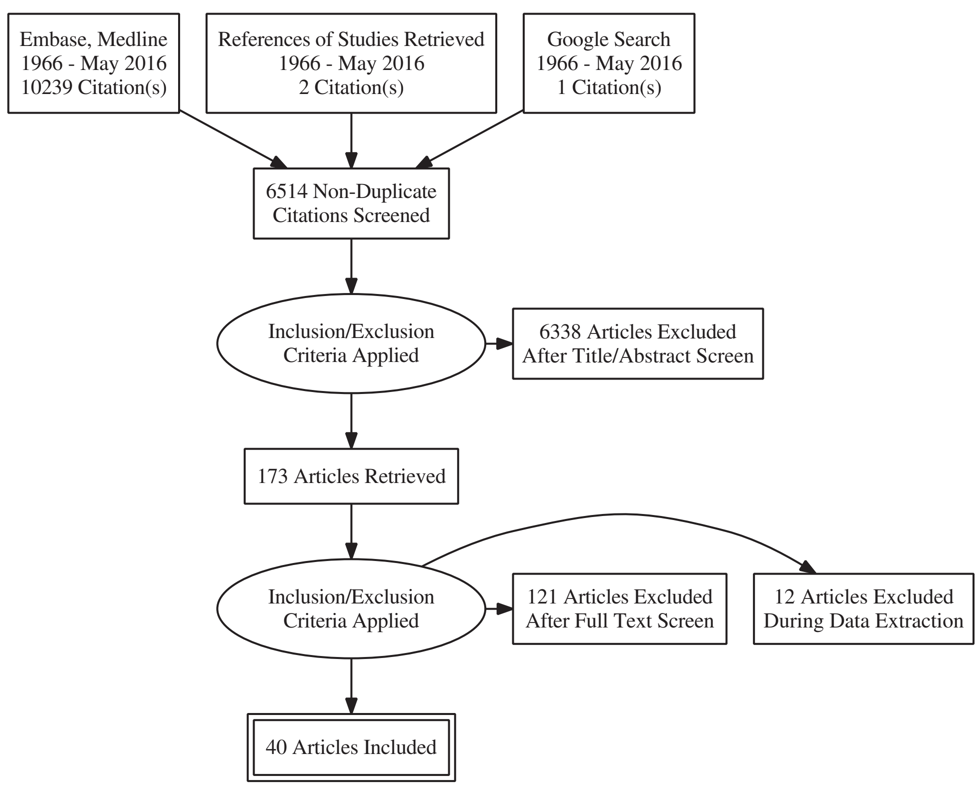

Figure 1 PRISMA flow diagram illustrating the process of selection of studies for inclusion in the systematic review.

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Table I **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	
Duval *et al.* (2015a) G	RCT
Karimzadeh and Javedani (2010)	RCT
Moran *et al.* (2011b)	RCT
Mutsaerts *et al.* (2016)	RCT
Palomba *et al.* (2010) G	RCT
Sim *et al.* (2014) G	RCT
Clark *et al.* (1998) G	Non-RCT
Crosignani *et al.* (2003)	Cohort
De Frene *et al.* (2015)	Cohort
Faure *et al.* (2014)	Cohort
Galletly *et al.* (1996a) G	Cohort
Galletly *et al.* (1996b) G	Cohort
Hakonsen *et al.* (2011)	Cohort
Hollman *et al.* (1996)	Cohort
Khaskheli *et al.* (2013)	Cohort
Mahoney (2014)	Cohort
Miller *et al.* (2008) G	Cohort
Salama *et al.* (2015)	Cohort
Reducing diet/healthy eating, weight-loss drugs, and exercise programme or advice	
Legro *et al.* (2015)	RCT
Lazurova *et al.* (2004)	Non-RCT
Kort *et al.* (2014)	Cohort
Reducing diet/health eating, or type of diet	
Becker *et al.* (2015)	RCT
Moran *et al.* (2003)	RCT
Qublan *et al.* (2007)	RCT
Turner-McGrievy *et al.* (2014)	RCT
Aliyeva *et al.* (1993)	Non-RCT
Palomba *et al.* (2008) G	Non-RCT
Awartani *et al.* (2012)	Cohort
Kiddy *et al.* (1992)	Cohort
Mavropoulos *et al.* (2005) G	Cohort
Thomson *et al.* (2009)	Cohort
Tsagareli *et al.* (2006)	Cohort
van Dam *et al.* (2004)	Cohort
Behavioural therapy, including motivational interviewing	
Karlsen *et al.* (2013)	Non-RCT
Koning (2015) C	Non-RCT
Homan *et al.* (2012)	Cohort
Exercise programme	
Thomson *et al.* (2008) G	RCT
Palomba *et al.* (2008)	Non-RCT
Orlistat	
Kumar and Arora (2014)	RCT
Metformin	
Karimzadeh and Javedani (2010)	RCT
Kumar and Arora (2014)	RCT
Qublan *et al.* (2007)	RCT
Sonmez *et al.* (2005)	RCT
Lazurova *et al.* (2004)	Non-RCT
Acarbose	
Sonmez *et al.* (2005)	RCT
Detailed lifestyle questionnaire	
Chavarro *et al.* (2012) C	Cohort

Continued

Table I *Continued*

G, group intervention; C, couples were able to take part.

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

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

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

Description of interventions

Table I provides brief details of the types of interventions tested. In general, interventions were poorly described, with insufficient detail to allow their replication. Where described, most reducing diets followed healthy eating principles by reducing fat and refined carbohydrate intake. Where available, studies described calorie intakes ranging from 1000 to 2000 kcal/d (depending on body size), apart from three studies that tested very low calorie diets as part of their reducing diets (Tsagareli *et al.*, 2006, Kiddy *et al.*, 1992, van Dam *et al.*, 2004) and one that tested a very low carbohydrate ketogenic diet (Mavropoulos *et al.*, 2005). If physical activity advice or programmes were incorporated into interventions, they were generally for aerobic exercise. There was no clear evidence that any particular regime was more effective for weight loss, providing there was a weight reduction diet prescribed.

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

Quality of studies

The quality of the studies included was variable. For full details of risk of bias assessment for the randomized studies please see

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Supplementary Table SII. Three of fourteen RCTs had four or five out of seven domains with low risk of bias, e.g. allocation concealment, incomplete outcome data, but the Lifestyle trial (Mutsaerts et al., 2016) stood out as the one with best quality. All studies were of high risk of bias with respect to blinding of participants to treatment allocation, and all had low risk of bias in at least two domains. Five of twenty-six non-randomized studies, having eight to nine of fourteen domains with low risk of bias, were judged to be good quality. Full details of the risk of bias assessment for the non-randomized studies are given in Supplementary Table SIII.

Studies involving female infertility participants

Pregnancy

Aggregated data from six RCTs show that women who received a combination of a reducing diet and exercise had higher pregnancy rates than those who underwent standard care, 238/434 (54.8%) versus 221/443 (49.9%); RR 1.59, 95% CI (1.01, 2.50) (Fig. 2). The trial by Mutsaerts *et al.* (2016) contributed significantly to the heterogeneity, I^2 = 71% and its exclusion in a *post hoc* sensitivity analysis reduced I^2–0%. Although the numbers of participants in other RCTs were too few for any meaningful conclusions to be drawn, a very small trial was unable to demonstrate any advantage of diet alone, while another suggested that orlistat might be beneficial. The results of an NRCT (Clark et al., 1998) support the result of the meta-analysis favouring diet and exercise. The study by Koning (2015) did not show any advantage associated with motivational interviewing.

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

Live births

Data from five RCTs (Fig. 3) did not favour diet and exercise over standard care in terms of live birth rates which were 48.9% (195/399) versus 46.8% (190/406), respectively; RR 1.54, 95% CI (0.93,

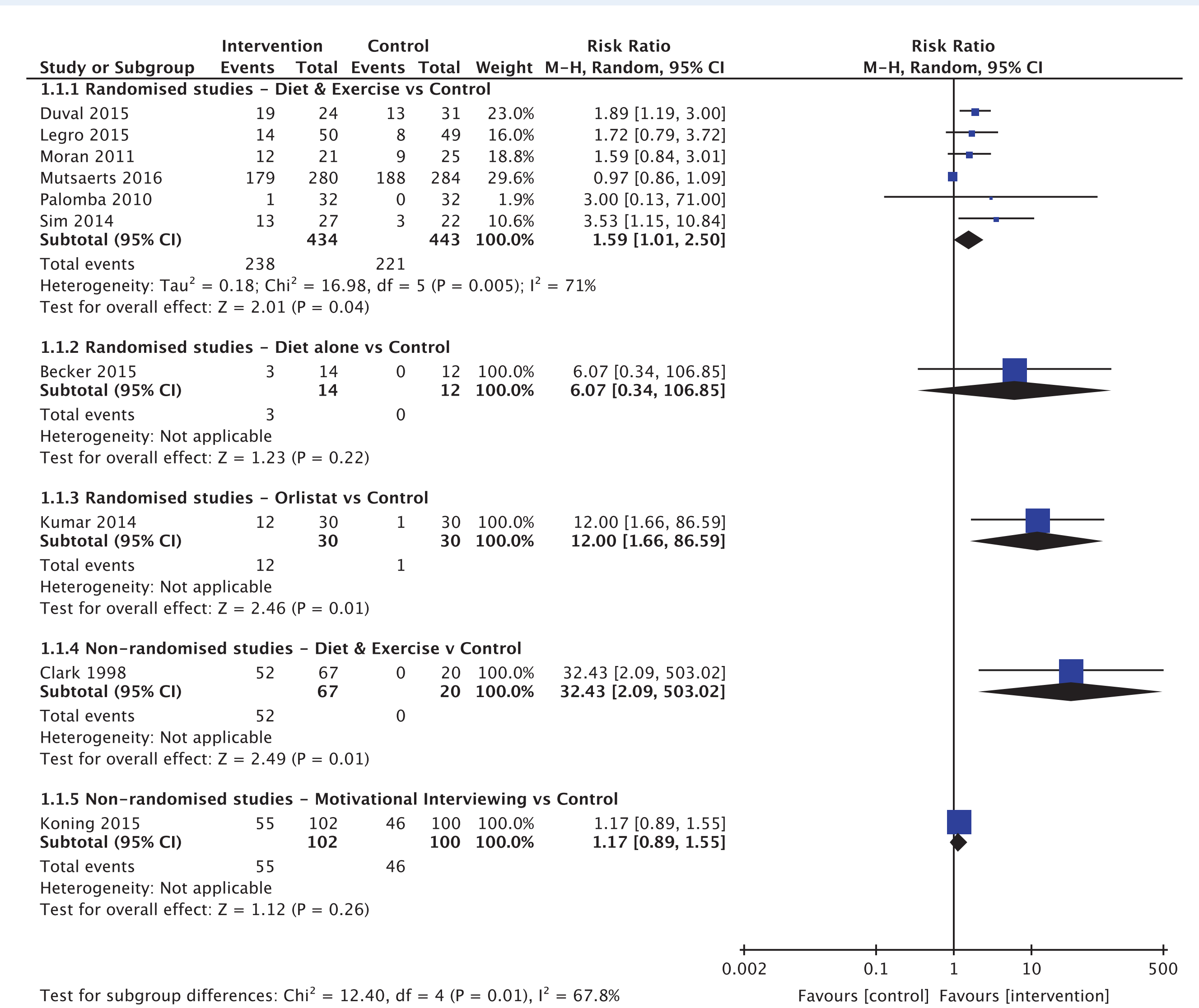

Figure 2 Forest plot—Pregnancies associated with diet, diet and exercise, orlistat and motivational interviewing versus control.

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Table II **Reproductive outcomes for women (lower numbers for ranking indicate better outcomes).**

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		TTC per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
Duval *et al.* (2015a)	Diet and exercise	24	1	79.2	2	62.5										
Clark *et al.* (1998)	Diet and exercise	67	2	77.6	1	67.2	13	14.9	9	18.2	1	89.6				
Kort *et al.* (2014)	Diet and exercise	52	3	65.4	4	48.1									4	226.57 days for those with 10&% weight loss
Mutsaerts *et al.* (2016)	Diet and exercise	280	4	63.9	3	53.2	12	14.6	12	22.9	17	42.4			3	Median 7.2 months (IQR 2.6, 12.0)
Khaskheli *et al.* (2013)	Diet and exercise	85	5	63.5	8	37.6	11	10.6	7	16.7						
Galletly *et al.* (1996b)	Diet and exercise	58	6	58.6												
Moran *et al.* (2011b)	Diet and exercise	18	7	57.1	7	38.9										
Koning (2015)	Motivational interviewing	102	8	53.9	5	47.1	2	2.0	2	3.6						
Chavarro *et al.* (2012)	Questionnaire	170	9	51.2												
Aliyeva *et al.* (1993)	Acupuncture	20	10	45.0							9	55.0	15	45.0		
Sim *et al.* (2014)	Diet and exercise	26	11	44.4	6	44.4	14	18.5	14	41.7						
Kumar and Arora (2014)	Orlistat	30	11	40.0							10	50.0				
Mavropoulos *et al.* (2005)	Low calorie ketogenic diet	5	13	40.0												
Palomba *et al.* (2008)	Exercise	20	14	35.0			7	5.0	5	14.3	5	65.0				
Homan *et al.* (2012)	Motivational interviewing	35	15	34.8			5	4.3	3	12.5						
Awartani *et al.* (2012)	Weight reduction advised	90	16	34.4												

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Table II *Continued*

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		TTC per participant (less = better)
		N	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**
Qublan *et al.* (2007)	Diet	24	17	33.3			4	4.2	3	12.5	10	50.0	11	61.9	
Legro *et al.* (2015)	Diet and exercise	50	18	32.0	9	26.0	9	6.0	10	18.8	6	60.3			
Crosignani *et al.* (2003)	Diet and exercise	33	19	30.3	10	24.2					8	55.6	6	66.7	
Aliyeva *et al.* (1993)	Diet	60	20	30.0							14	46.7	8	63.3	
Kiddy *et al.* (1992)	Very low calorie diet/low calorie diet	24	21	29.2	14	16.7	10	8.3	13	28.6			20	29.4	
Hollman *et al.* (1996)	Diet and exercise	35	22	28.6	12	22.9	8	5.7	11	20.0			3	80.0	
Legro *et al.* (2015)	Diet, exercise, oral contraceptive pill	50	23	28.0	11	24.0	3	4.0	5	14.3	4	67.1			
Qublan *et al.* (2007)	Metformin	22	24	27.3			6	4.5	7	16.7	15	45.5	12	61.1	
Kumar and Arora (2014)	Metformin	30	25	26.7							20	23.3			
Becker *et al.* (2015)	Diet	14	26	21.4	13	21.4									
Karimzadeh and Javedani (2010)	Diet and exercise	75	26	20.0									6	66.7	
Lazurova *et al.* (2004)	Metformin	30	28	20.0									4	70.0	
Miller *et al.* (2008)	Diet and exercise	12	29	16.7									1	83.3	
Karimzadeh and Javedani (2010)	Metformin and clomiphene	88	30	14.8									10	62.5	
De Frene *et al.*, (2015)	Diet and exercise	23	31	13.0											
Karimzadeh and Javedani (2010)	Metformin	90	32	12.2									13	55.6	

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Table II *Continued*

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		TTC per participant (less = better)	
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	
Salama *et al.* (2015)	Mediterranean diet and exercise	58	33	12.1									9	62.8		
Turner-McGrievy *et al.* (2014)	Low calorie diet	9	34	11.1							22	0.0				
Palomba *et al.* (2008)	Diet	20	35	10.0			1	0.0	1	0.0	19	25.0				
Galletly *et al.* (1996a)	Exercise and advice	96	36	9.4												
Moran *et al.* (2003)	High-protein diet	14	37	8.7									21	26.1	1	4–5 weeks
Lazurova *et al.* (2004)	Sibutramine, diet, exercise	15	38	6.7									14	53.3		
Thomson *et al.* (2008)	Diet and aerobic exercise	31	39	6.3							10	50.0	17	42.9		
Moran *et al.* (2003)	Low-protein diet	14	40	4.3									22	22.7	1	4–5 weeks
Thomson *et al.* (2008)	Diet	30	41	3.3							10	50.0	24	21.4		
Palomba *et al.* (2010)	Diet and exercise, Clomiphene	32	42	3.1							18	37.5	19	34.4		
Thomson *et al.* (2008)	Diet and aerobic and resistance exercise	33	43	3.0							16	42.8	16	44.4		
Turner-McGrievy *et al.* (2014)	Vegan diet	9	44	0							22	0.0				
Sonmez *et al.* (2005)	Acarbose	15									2	86.7	5	69.2		
Sonmez *et al.* (2005)	Metformin	15									3	80.0	2	80.0		
van Dam *et al.* (2004)	Very low calorie diet	15									6	60.0				

Continued

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Table II *Continued*

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		TTC per participant (less = better)
		N	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank
Thomson *et al.* (2009)	Diet	52									20	19.2	18	42.3	
Palomba *et al.* (2010)	Diet and exercise	32									21	12.5	25	12.5	
Mahoney (2014)	Motivational interviewing, diet, exercise												23	22.2	

TTC, time to conception; IQR, interquartile range.

2.56). Mutsaerts *et al.* (2016) again contributed significantly to the heterogeneity, $I^2 = 69\%$. Its exclusion in a *post hoc* sensitivity analysis reduced I^2–0%, and resulted in diet and exercise having a statistical advantage, RR 1.86, 95% CI (1.25, 2.77). The NRCT (Clark *et al.*, 1995, 1998) also favoured the intervention arm, 45/67 (67.2%) versus no treatment (0/20); RR 28.10, 95% CI (1.81, 436.85). Motivational interviewing was also not associated with an increased live birth rate.

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

Natural and IVF conceptions

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

Miscarriages

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

Ovulation

One RCT (Palomba *et al.*, 2010) found a 37.5% (12/32) ovulation improvement with a combination of reducing diet and exercise, while its control group had a 9.3% (3/32) improvement rate; RR 4.00 95% CI (1.25, 12.84) (Fig. 8). An NRCT, also using diet and exercise, had the highest rate of improvement of all included studies in its intervention group, 89.6% (60/67), while none of the participants in the control group saw improvement; RR 37.37, 95% CI (2.41, 578.65).

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

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

Another RCT (Thomson *et al.*, 2008) randomized its participants, who had PCOS, to receive an energy-restricted high-protein diet alone (DO), combined with aerobic exercise (DA) or combined with both aerobic and resistance exercise (DC). DO saw a 50% (6/

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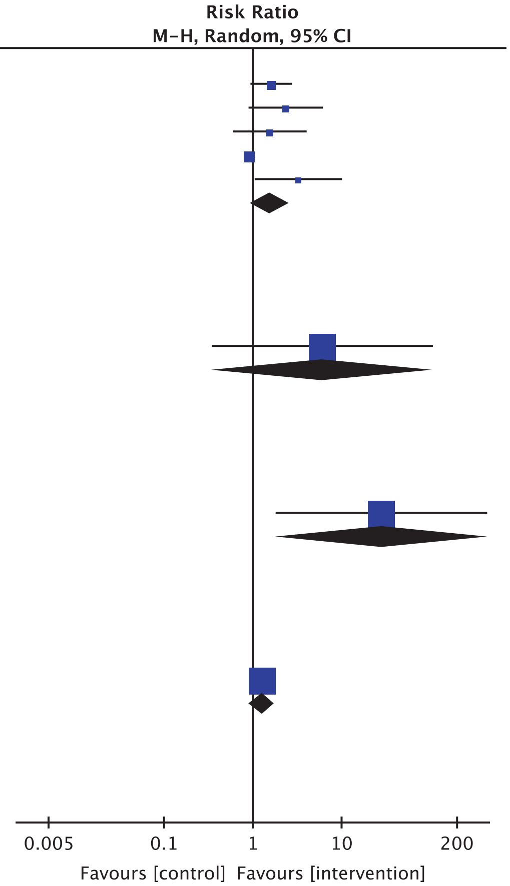
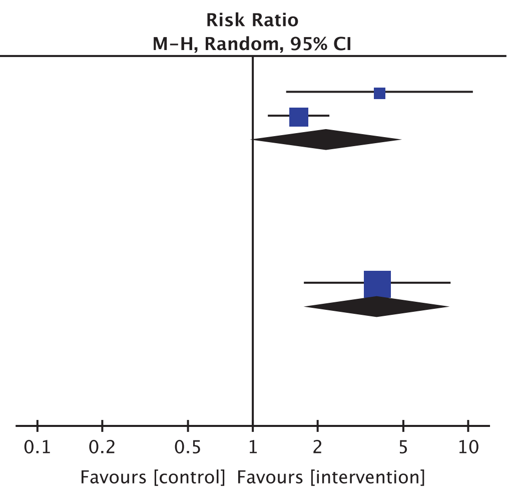
Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Randomised studies - Diet & Exercise vs Control						
Duval 2015	15	24	12	31	24.3%	1.61 [0.94, 2.77]
Legro 2015	12	50	5	49	15.1%	2.35 [0.90, 6.18]
Moran 2011	7	18	5	20	15.3%	1.56 [0.60, 4.04]
Mutsaerts 2016	149	280	165	284	32.7%	0.92 [0.79, 1.06]
Sim 2014	12	27	3	22	12.5%	3.26 [1.05, 10.12]
Subtotal (95% CI)		**399**		**406**	**100.0%**	**1.54 [0.93, 2.56]**
Total events	195		190			
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 12.91$, df = 4 (P = 0.01); $I^2 = 69\%$						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.2.2 Randomised studies - Diet vs Control						
Becker 2015	3	14	0	12	100.0%	6.07 [0.34, 106.85]
Subtotal (95% CI)		**14**		**12**	**100.0%**	**6.07 [0.34, 106.85]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.2.3 Non-randomised studies - Diet & Exercise vs Control						
Clark 1998	45	67	0	20	100.0%	28.10 [1.81, 436.85]
Subtotal (95% CI)		**67**		**20**	**100.0%**	**28.10 [1.81, 436.85]**
Total events	45		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.38 (P = 0.02)						
1.2.4 Non-randomised studies - Motivational Interviewing vs Control						
Koning 2015	48	102	37	100	100.0%	1.27 [0.92, 1.77]
Subtotal (95% CI)		**102**		**100**	**100.0%**	**1.27 [0.92, 1.77]**
Total events	48		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						



Test for subgroup differences: $Chi^2 = 6.06$, df = 3 (P = 0.11), $I^2 = 50.5\%$

Figure 3 Forest plot—Intervention versus control: live births.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Randomised studies - Diet & Exercise vs Control						
Duval 2015	12	24	4	31	34.6%	3.88 [1.43, 10.51]
Mutsaerts 2016	74	280	46	284	65.4%	1.63 [1.17, 2.27]
Subtotal (95% CI)		**304**		**315**	**100.0%**	**2.20 [0.98, 4.93]**
Total events	86		50			
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 2.60$, df = 1 (P = 0.11); $I^2 = 62\%$						
Test for overall effect: Z = 1.92 (P = 0.06)						
1.7.2 Non-randomised studies - Motivational interviewing vs Control						
Koning 2015	27	102	7	100	100.0%	3.78 [1.73, 8.28]
Subtotal (95% CI)		**102**		**100**	**100.0%**	**3.78 [1.73, 8.28]**
Total events	27		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.32 (P = 0.0009)						



Test for subgroup differences: $Chi^2 = 0.89$, df = 1 (P = 0.35), $I^2 = 0\%$

Figure 4 Forest plot—Intervention versus control: natural conceptions.

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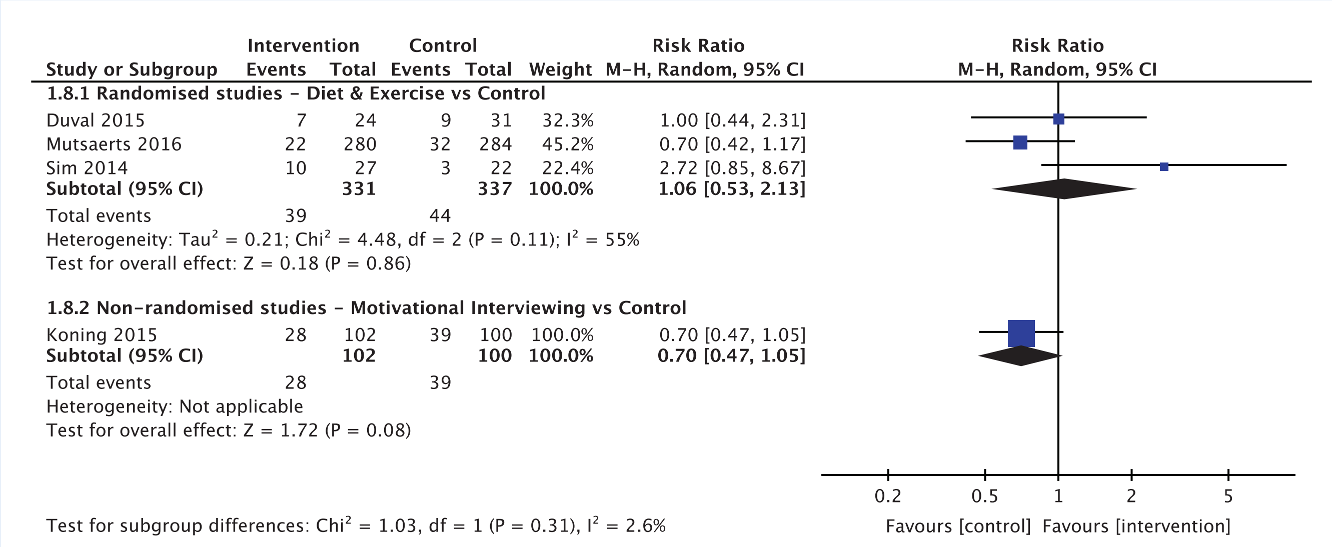

Figure 5 Forest plot—Intervention versus control: IVF conceptions.

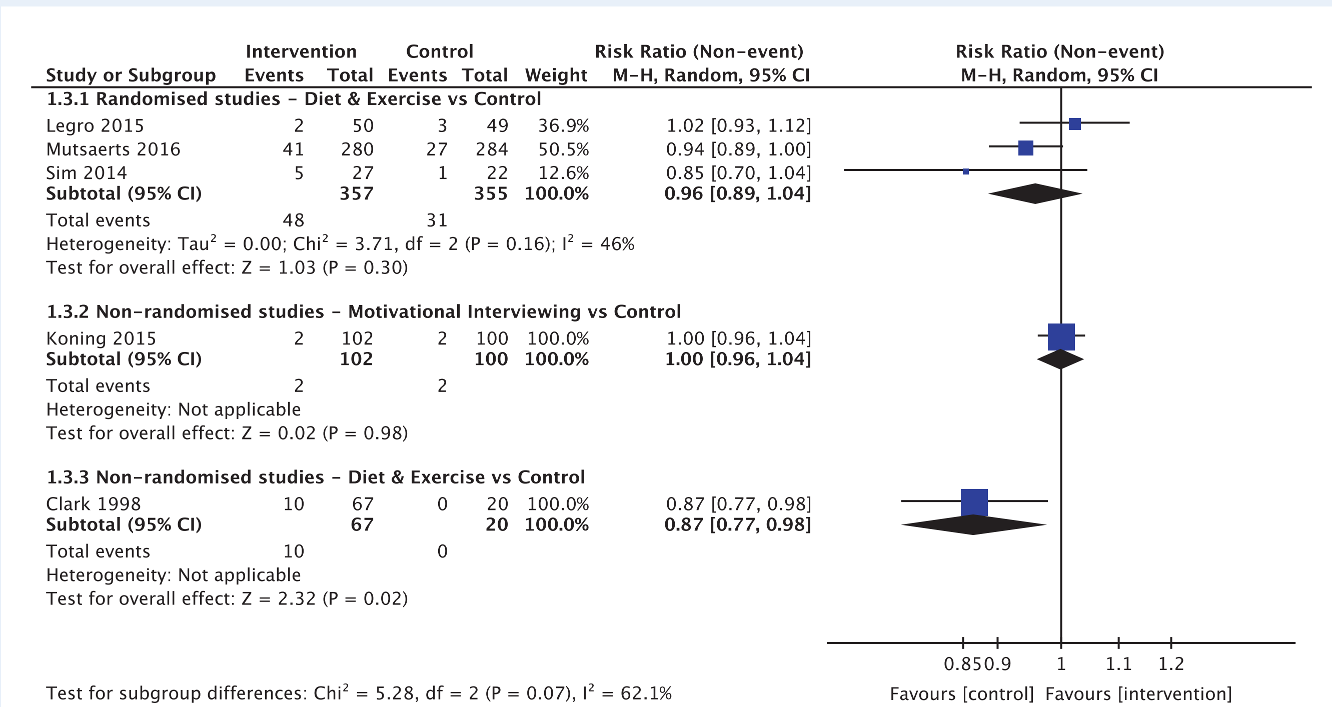

Figure 6 Forest plot—Intervention versus control: miscarriages for all participants enroled.

12) improvement in ovulation, DA a 50% (3/6) improvement, and DC a 42.8% (3/7) improvement.

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

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

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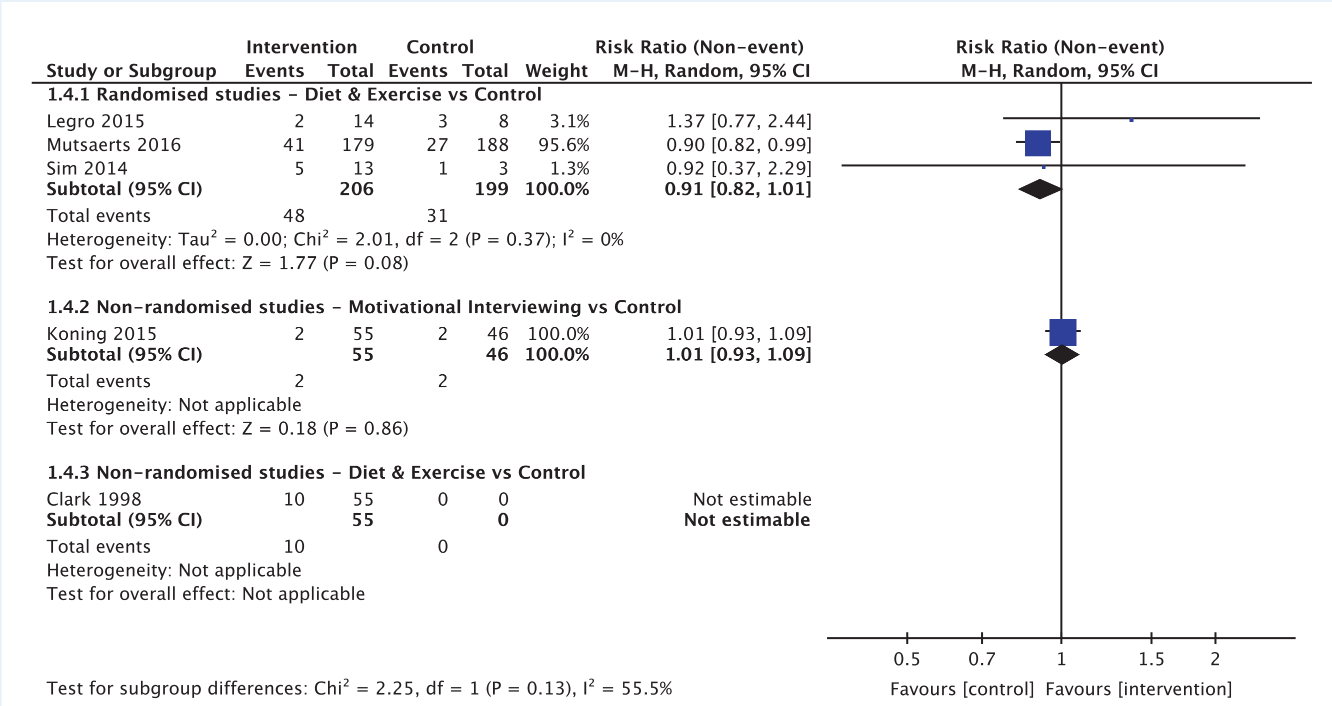

Figure 7 Forest plot—Intervention versus control: miscarriages for women who became pregnant.

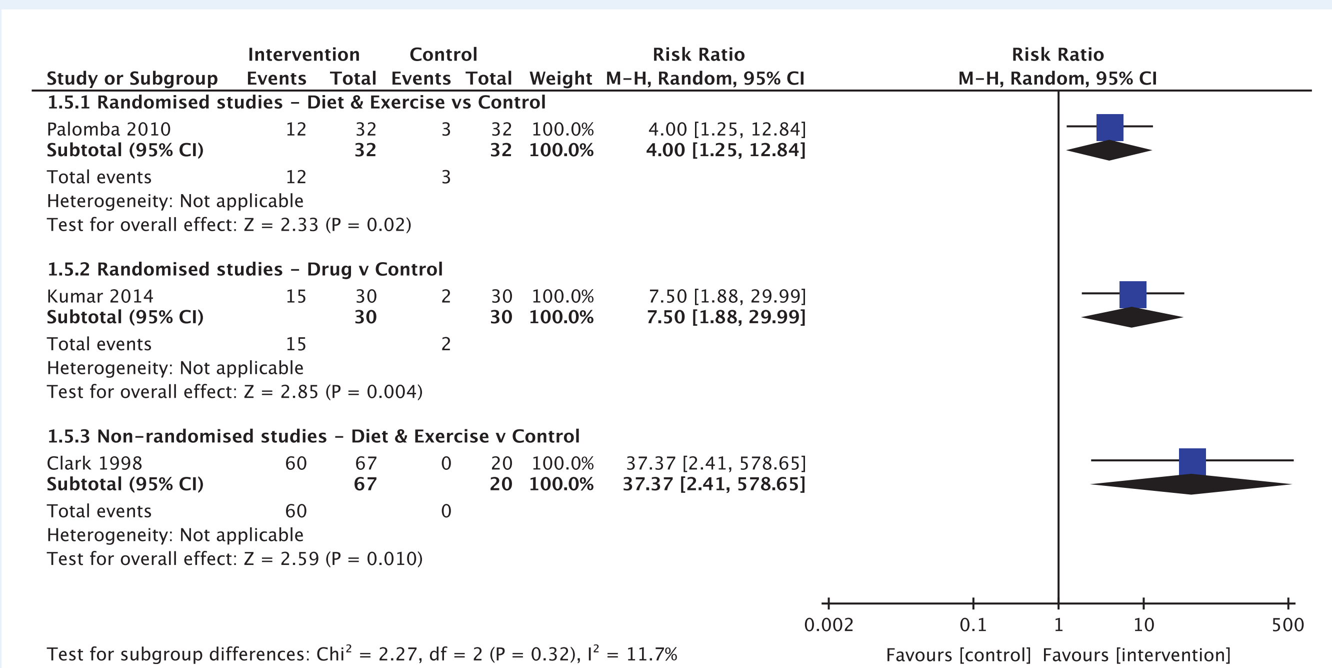

Figure 8 Forest plot—Intervention versus control: ovulation improvement.

Menstrual irregularity

In clomiphene citrate resistant PCOS women, a single trial (Palomba *et al.*, 2010), showed that hypocaloric diet and exercise was significantly more likely to result in menstrual improvement, than observation only: 34.4% (11/32) versus 9.3% (3/32); RR 3.67, 95% CI (1.13, 11.92) (Fig. 9). Other studies without control groups also suggest that diet and exercise were associated with improvement in menstrual regularity (Table II). There were no RCTs evaluating the

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role of dietary interventions alone or motivational interviewing in regulating menstrual cyclicity. Data from observational and often uncontrolled studies of other interventions show variable levels of success (Table II).

Oocyte retrieval

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

Time to conception

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

Weight loss

Aggregated data from RCTs suggest that a combination of a reducing diet and exercise resulted in greater weight loss than that achieved in control groups (Fig. 11); mean difference -3.98 kg (95% CI −4.85, −3.12). Diet alone was also shown to be more effective in a small RCT; mean difference −5.23 kg (95% CI −7.42, −3.04) (Becker *et al.*, 2015).

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

Comparisons with metformin

Pregnancy

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

Ovulation

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

Menstrual irregularity

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

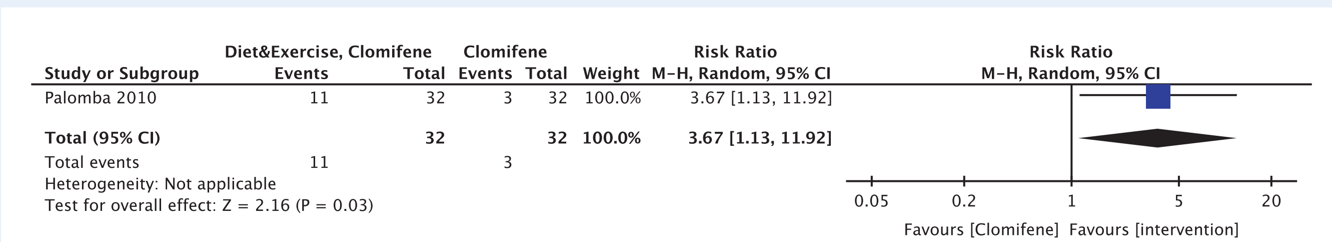

Figure 9 Forest plot—Intervention versus control: improvement of menstrual irregularity.

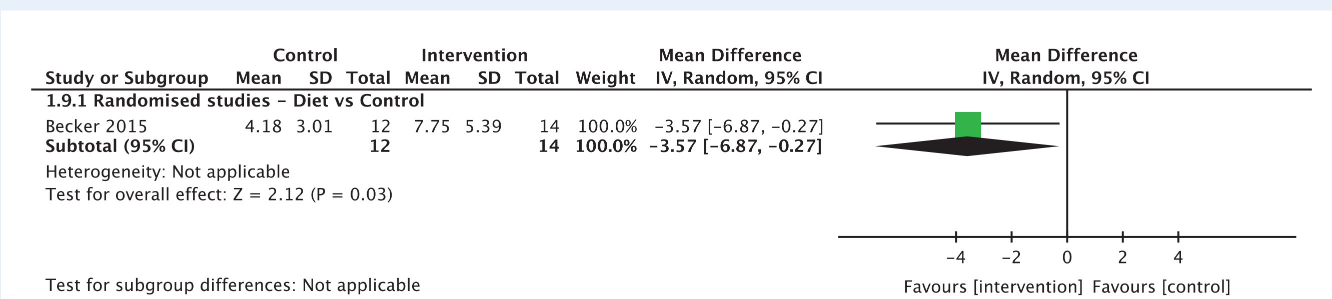

Figure 10 Forest plot—Intervention versus control: oocytes retrieved per female participant.

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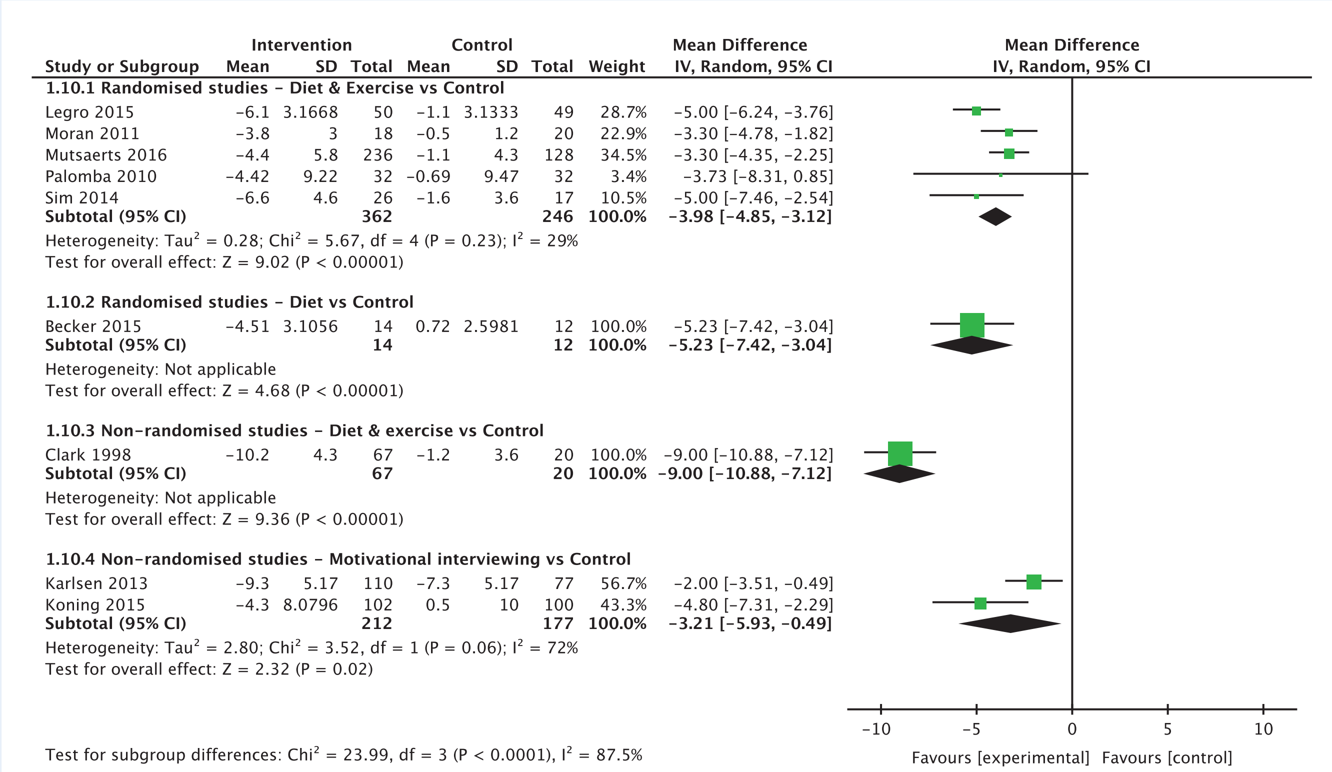

Figure 11 Forest plot—Intervention versus control: change in weight (kg).

Weight loss

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

Summary of the key findings in infertile women

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

Barriers to weight loss in infertile women

Very little has been reported regarding the perceived barriers to weight loss in overweight and obese infertile women. Two of the included studies attempted in some way to evaluate these.

In the trial by Thomson *et al.* (2008), 104 participants were allocated to receive an energy-restricted diet only (DO), the same diet combined with five sessions of aerobic walking and jogging exercise per week (DA), or the diet combined with aerobic and resistance training exercises (DC), where resistance exercise replaced two of the aerobic sessions. Forty-three of the participants in the trial (DO = 13, DA = 11 and DC = 19) completed a validated Exercise Benefits/Barriers Scale at weeks 0, 10 and 20 (Thomson *et al.*, 2016). This was to determine their perceptions of the benefits and barriers to participation in exercise. The scale included 43 items with statements related to ideas about exercise and a four-point Likert scale, with 4 = strongly agree, 3 = agree, 2 = disagree and 1 = strongly disagree. At baseline, the statements with the highest agreement were 'exercise tires me' [mean (SD), 2.86 (0.71)]; 'exercise is hard work for me [2.79 (0.67)], and 'I am fatigued by exercise' [2.60 (0.62)]. Those with the lowest agreement were: 'my family members do not encourage me to exercise' [1.56 (0.59)], 'my spouse does not encourage exercising' [1.63 (0.70)] and 'I think people in exercise clothes look funny' [1.72 (0.59)].

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

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

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

Study ID	Intervention arm	*N*	Mean weight change (kg) per participant		Mean BMI change (kg/m^2) per participant		Mean waist circumference change (cm) per participant	
			Rank	Change	Rank	Change	Rank	Change
Mavropoulos *et al.* (2005)	Low calorie ketogenic diet	5	1	−12.34 ± 6.37	8	−4.0		
Hollman *et al.* (1996)	Diet and exercise	35	2	−10.2 ± 7.9	10	−3.4 (median)		
Clark *et al.* (1998)	Diet and exercise	67	3	−10.2 ± 4.3	9	−3.7 ± 1.6		
Thomson *et al.* (2008)	Diet and aerobic exercise	31	4	−10.1 ± 5.6			1	−11.7 ± 6.1
Karlsen *et al.* (2013)	Motivational interviewing	110	5	−9.3	11	−3.3		
Thomson *et al.* (2009)	Diet	52	6	−9.0 ± 0.8 (SEM)			4	−10.4 ± 0.9 (SEM)
Thomson *et al.* (2008)	Diet	30	7	−8.6 ± 6.0			3	−10.8 ± 7.1
Thomson *et al.* (2008)	Diet and aerobic and resistance exercise	3	8	−8.6 ± 5.2			2	−11.0 ± 6.3
Moran *et al.* (2003)	High-protein diet	14	9	−8.5 ± 1.1				
Kumar and Arora (2014)	Orlistat	30	10	−7.81 ± 0.66%	4	−8.12 ± 6.71%		
Kumar and Arora (2014)	Metformin	30	11	−7.78 ± 0.57% (SEM)	3	−8.40 ± 0.65% (SEM)	14	−2.68 ± 0.16% (SEM)
Kiddy *et al.* (1992)	Very low calorie diet/low calorie diet	24	12	−6.9 ± 6.7				
Moran *et al.* (2003)	Low-protein diet	14	13	−6.9 ± 0.8 (SEM)				
Sim *et al.* (2014)	Diet and exercise	26	14	−6.6 ± 4.6	14	−2.4 ± 1.6	6	−8.7 ± 5.6
Salama *et al.* (2015)	Mediterranean diet and exercise	58	15	−6.3 ± 20.8	16	−2.37 ± 7.28	7	−6.45 ± 14.13
Legro *et al.* (2015)	Lifestyle	50	16	−6.2, 95% CI (−7.3, −5.3)			8	−6.3, 95% CI (−9.2, −3.4)
Galletly *et al.* (1996b)	Diet and exercise	58	17	−6.2 ± 4.5	13	−2.4 ± 1.7		
Legro *et al.* (2015)	Diet, exercise, oral contraceptive pill	50	18	−6.1, 95% CI (−7.0, −5.2)			9	−6.2, 95% CI (−9.1, −3.3)
Tsagareli *et al.* (2006)	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
Galletly *et al.* (1996a)	Diet and exercise	96	20	−5.2 ± 5.1				
Becker *et al.* (2015)	Diet	14	21	−4.51 ± 0.83 (SEM)			15	−1.31 ± 10.5
Palomba *et al.* (2010)	Diet and exercise, clomiphene	32	22	−4.42 ± 9.22	12	−2.64 ± 4.26	11	−4.92 ± 5.87
Mutsaerts *et al.* (2016)	Diet and exercise	280	23	−4.4 ± 5.8	21	−1.3 (Median) IQR (−2.5, −0.07)		
Koning (2015)	Motivational interviewing	102	24	−4.3 ± 0.8 (SEM)	20	−1.4 ± 0.3 (SEM)		
Palomba *et al.* (2010)	Diet and exercise	32	25	−4.21 ± 8.56	15	−2.39 ± 3.54	12	−3.84 ± 6.35
Moran *et al.* (2011b)	Diet and exercise	18	26	−3.8 ± 3.0	19	−1.4 ± 1.1	10	−5.3 ± 4.6
Mahoney (2014)	Motivational interviewing, diet, exercise	9	27	−3.18 ± 2.27	24	−0.7 ± 7.31		

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Table III *Continued*

Study ID	Intervention arm	*N*	Mean weight change (kg) per participant		Mean BMI change (kg/m^2) per participant		Mean waist circumference change (cm) per participant	
			Rank	Change	Rank	Change	Rank	Change
Turner-McGrievy *et al.* (2014)	Vegan diet	9	28	−2.1 ± 3.5				
Turner-McGrievy *et al.* (2014)	Low calorie diet	9	29	−0.4 ± 0.9				
Chavarro *et al.* (2012)	Questionnaire	170	30	&0.3 (Median) IQR (−0.1, 1.8)				
Kort *et al.* (2014)	Diet and exercise	52			1	−13.89% ± 3.71% in 17 with 10&% weight loss −3.79% ± 3.98% in 35 with < 10% weight loss		
Khaskheli *et al.* (2013)	Diet and exercise	85			2	−9.6 ± 1.23		
Lazurova *et al.* (2004)	Sibutramine, diet, exercise	15			5	−4.6 ± 4.2 (SEM)		
Qublan *et al.* (2007)	Diet	24			6	−4.8		
Qublan *et al.* (2007)	Metformin	22			7	−4.1		
Miller *et al.* (2008)	Diet and exercise	12			18	−2.06 ± 0.51 (SEM)		
Sonmez *et al.* (2005)	Acarbose	15			22	−1.1 ± 2.78		
Lazurova *et al.* (2004)	Metformin	30			23	−0.85 ± 0.38 (SEM)		
Sonmez *et al.* (2005)	Metformin	15			25	−0.3 ± 2.47		
Homan *et al.* (2012)	Motivational interviewing	35		'47% of the overweight participants had a modest loss of between 1 and 5 kg (not statistically significant)'				−3.8 in½ of those attending follow-up and not pregnant
Duval *et al.* (2015a)	Diet and exercise	24		10/24 had ≥5% weight loss (compared to 11/31 in control group)				12/24 had ≥5 cm reduction (compared to 11/31 in control group)
Karimzadeh and Javedani (2010)	Diet and exercise	75						Significantly lower waist circumference ($P = 0.001$) in the lifestyle group than in the clomiphene, metformin and clomiphene/metformin groups
Aliyeva *et al.* (1993)	Diet	60		'30–40% decrease in body weight in 2–4 months'				
Aliyeva *et al.* (1993)	Acupuncture	20		'Slower rate and extent of weight reduction: 7–9 months'				
Awartani *et al.* (2012)	Weight reduction advised	90				23/90 reduced their BMI below 35; 65/90 did not		

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Table III *Continued*

Study ID	Intervention arm	N	Mean weight change (kg) per participant		Mean BMI change (kg/m^2) per participant		Mean waist circumference change (cm) per participant	
			Rank	Change	Rank	Change	Rank	Change
Crosignani et al. (2003)	Diet and 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
van Dam et al. (2004)	Very low calorie diet	15		14/15 loss at least 10% of body weight				
Palomba et al. (2008)	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%
Palomba et al. (2008)	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%

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

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 personalized 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 IV). 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.

Improvement in semen analysis parameters

A cohort of 44 men with BMI 33–61 kg/m^2 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 IV.

Change in weight

Table IV also summarizes the weight loss achieved in both studies.

Summary

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

Discussion

Key findings

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

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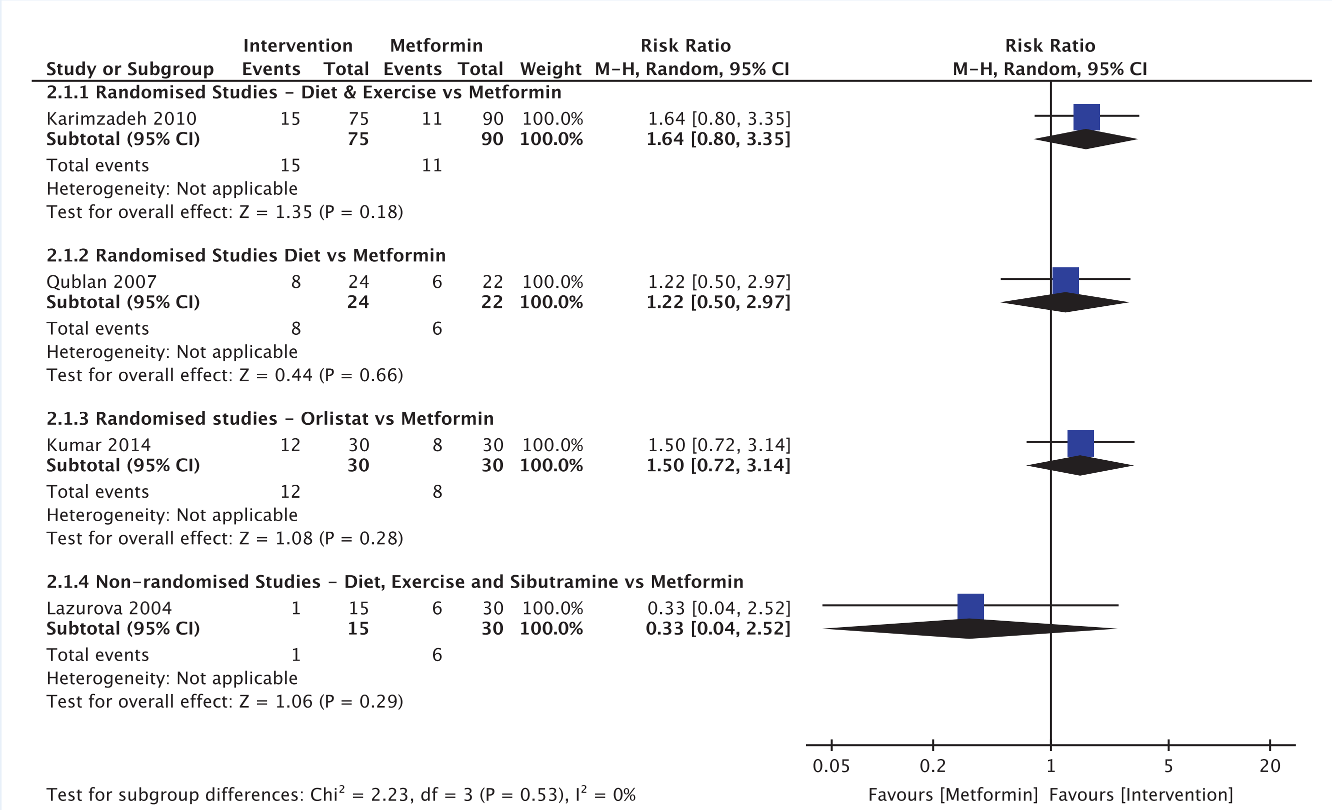

Figure 12 Forest plot—Intervention versus metformin: women who became pregnant.

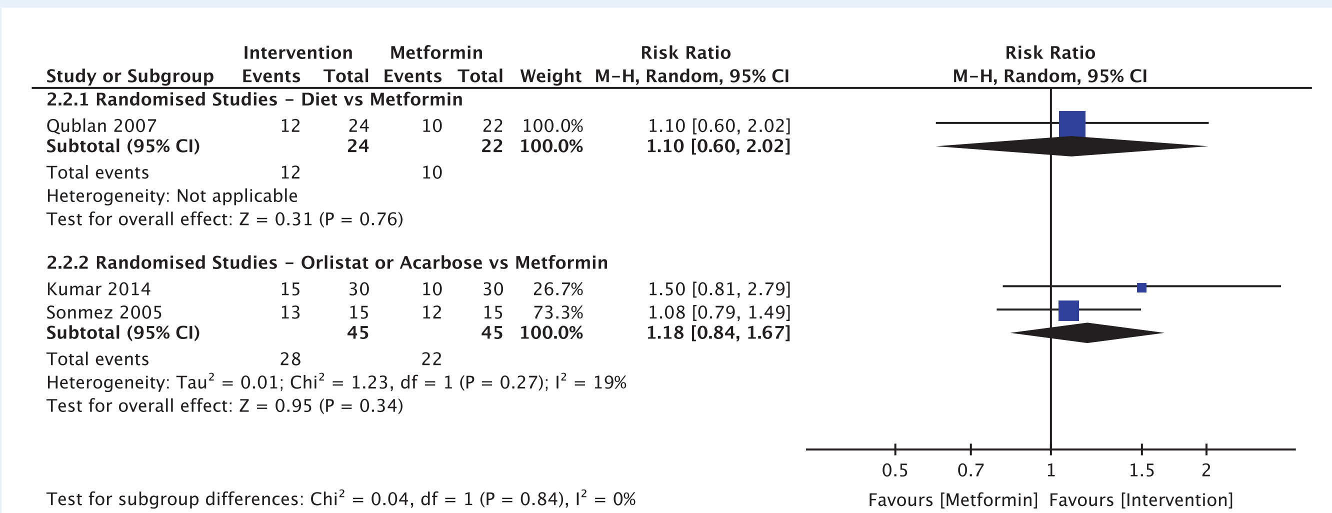

Figure 13 Forest plot—Intervention versus metformin: improvement in ovulation.

Women

Pregnancies and live births

Weight loss interventions, particularly those with reducing diets and exercise, were more likely than controls to result in pregnancy. Live births were reported by relatively fewer studies, usually involving women undergoing fertility treatments such as OI or IVF. Data from studies predating the Lifestyle trial in 2016 (Mutsaerts *et al.*, 2016) suggested that diet and exercise combinations were superior to standard care, but inclusion of this trial changed this. Those in the intervention arm underwent a 6-month programme based on diet and exercise, prior to undergoing 18 months of fertility treatments.

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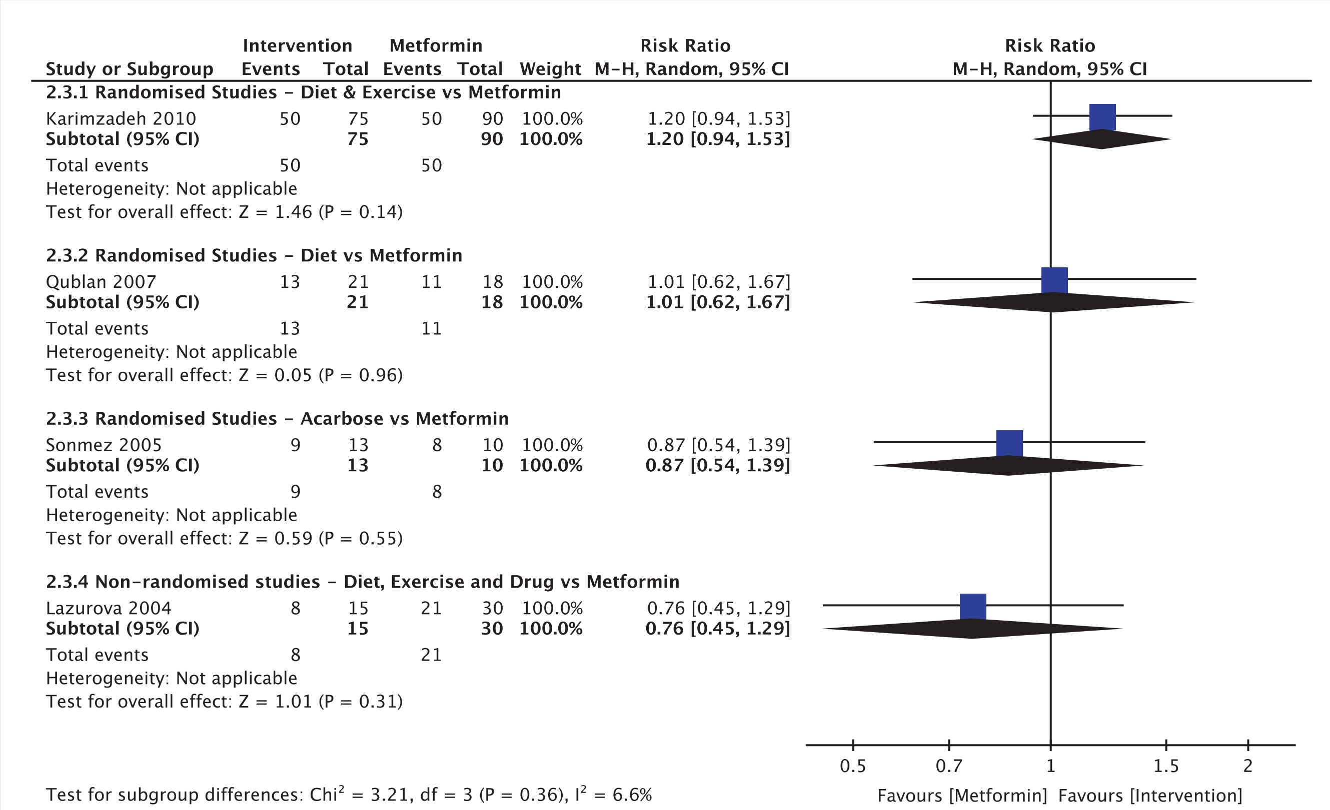

Figure 14 Forest plot—Intervention versus metformin: improvement in menstrual irregularity per irregular menstruating female participant.

Those in the control arm commenced fertility treatments immediately. The primary outcome was vaginal birth of a healthy singleton of at least 37 weeks' gestation within 24 months after randomization. The trial was well conducted, with low risk of bias. This was the largest study in the review, and it carried substantial weight during meta-analysis. The results deviated from the trend exhibited by the preceding trials, resulting in marked increase in heterogeneity. It is possible that the results might have been different if the control group underwent 6 months of no intervention observation prior to 18 months of treatment. The trial found that significantly more women in the intervention group had ongoing pregnancies from natural conception than the control group, consistent with our other findings.

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

Miscarriages

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

Ovulation

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

Menstrual irregularity

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

Natural and IVF conceptions

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

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Table IV Reproductive and weight outcomes for infertile men.

	Faure *et al.* (2014) *N* = 8	Hakonsen *et al.* (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: Weight loss 3.5–12.1%		Group 1 ($n = 9$) Mean −11 95% CI −49, 27
Group 2: Weight loss 12.2–17.1%		Group 2 ($n = 9$) Mean +19 95% CI −23, 61
Group 3: Weight loss 17.2–25.4%		Group 3 ($n = 9$) Mean +17 95% CI −24, 58
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^2)	Mean −1.22 SD 1.38	
Change in Waist circumference (cm)	Mean −8.50 SD 7.89	

Change in weight, BMI and waist circumference

No class of intervention was consistently better in achieving reduction in weight compared to others. Trials with longer interventions and follow-up sometimes suffered from higher rates of study drop-out, for example 20.4% in the 12-month Sim *et al.* RCT (Sim *et al.*, 2014a) and 10.6% in the 6-month Mutsaerts *et al.* RCT (Mutsaerts *et al.*, 2016), both of which mainly had diet and exercise. Others had no drop-out: Karlsen *et al.* after 7–8 months (Karlsen *et al.*, 2013) and Koning after 6 months (Koning, 2015), and both included motivational interviewing. This suggests that enhancing motivation plays a key role in compliance. Programmes with strict dietary and exercise modifications may be more likely to see discontinuation. The study with the most weight lost, the cohort study by Mavropoulos *et al.* (2005), utilized a very restrictive diet for 6 months, and had very low recruitment ($n = 11$) and a high rate of drop-out (58.5%).

Metformin

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

Interventions in infertile men

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

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Types of diet

As expected, the dietary interventions used were based on caloric restriction, and were usually consistent with weight reduction advice from national guidelines (National Clinical Guideline Centre, 2014; Dietz et al., 2015). It is hard to say, based on the data obtained, whether any particular degree of restriction was superior for achievement of weight loss, particularly given the frequent pairing of diet with exercise. Some of the RCTs used individualized diets, tailoring caloric deficit to baseline weight (Becker et al., 2015; Duval et al., 2015b). Others mentioned a hypocaloric range within which dietary intakes would fall (Qublan et al., 2007; Thomson et al., 2008; Kumar and Arora, 2014; Turner-McGrievy et al., 2014), generally between 1200 and 1800 kcal/day. Dieticians were used to assist with dietary advice in a few cases (Thomson et al., 2008; Turner-McGrievy et al., 2014; Duval et al., 2015b; Mutsaerts et al., 2016). The RCT with the lowest recruitment and highest discontinuation rate used a vegan diet in one of its study arms (Turner-McGrievy et al., 2014), suggesting poor acceptance.

Types of exercise

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

Types of weight-loss medication

The use of weight loss drugs is contraindicated during pregnancy (Department of Veterans Affairs, 2014), and the studies using them aimed to reduce weight prior to attempting pregnancy. One trial (Legro et al., 2015) recommended barrier contraception during its intervention. Oral medications used in the studies included orlistat, a lipase inhibitor; sibutramine, a selective serotonin and norepinephrine reuptake inhibitor; and acarbose, an alpha-glucosidase inhibitor shown to induce modest weight loss, though not suitable for weight maintenance (Hauner et al., 2001). Of these, sibutramine, which has been withdrawn in Europe and the USA but is still available on the internet, has been shown in a large study to have a risk of cardiovascular defects in unborn infants (Källén, 2014), while the same study showed no risk of birth defects from orlistat use. The safety of acarbose in pregnancy is not established. Orlistat was shown to be superior to a control with respect to achievement of pregnancy and ovulation in a single study (Kumar and Arora, 2014). Until further evidence is available, lifestyle interventions should still be considered the first line therapy, with drug use reserved for monitored trials.

Strengths and limitations of the review

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

Clinical recommendations

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

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

Research recommendations

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

A reasonable control intervention would be the administration of dietary and exercise advice only, to be undertaken for a brief period to reduce persons allocated to this arm feeling as though their fertility treatments were being delayed with no intervention. Similar durations employed between intervention and control groups prior to starting fertility treatments would allow for fair comparisons with respect to weight loss and reproductive outcomes.

A long duration of follow-up, spanning decades, might answer further questions, including whether obstetric problems related to weight such as gestational diabetes or caesarean rates might be reduced in imminent or future pregnancies. The permanency of lifestyle changes made while attempting fertility might also be established, as well as their impact on family members, and the maintenance of weight loss in the long-term.

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Conclusions

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

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

Dr D.B. was involved in design and conduct of the review, data analysis, drafting the manuscript and critical discussion. Professor A.A. was involved in the design and conduct of the review, supervised data analysis, checked data extraction and was involved in manuscript revision and critical discussion. Professor S.B. was involved in the design of the review and contributed to manuscript revision and critical discussion.

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Conflict of interest

None declared.

References

Anonymous. National Collaborating Centre for Women's and Children's Health (UK). Ectopic Pregnancy and Miscarriage. 2012. RCOG.

Aliyeva EA, Fanchenko ND, Parshutin NP, Gasparov AS, Pshenichnikova TI. The effect of a decrease in body weight in patients with the polycystic ovary syndrome. *Akush Ginekol* 1993;**3**:33–36.

Awartani K, Al-Sahan N, Al-Hassan S, Coskun S. Effect of weight loss in morbidly obese infertile women on IVF outcome. *Fertil Steril* 2012;**3**:S204.

Balen A, Dresner M, Scott E, Drife J. Should obese women with polycystic ovary syndrome receive treatment for infertility? *BMJ* 2006a;**332**:434–435.

Balen A, Platteau P, Andersen A, Devroey P, Sorensen P, Helmgaard L, Arce C. The influence of body weight on response to ovulation induction with gonadotrophins in 335 women with World Health Organization group II anovulatory infertility. *BJOG* 2006b;**10**:1195–1202.

Becker GF, Passos EP, Moulin CC. Short-term effects of a hypocaloric diet with low glycemic index and low glycemic load on body adiposity, metabolic variables, ghrelin, leptin, and pregnancy rate in overweight and obese infertile women: a randomized controlled trial. *Am J Clin Nutr* 2015;**6**:1365–1372.

Bellver J, Ayllon Y, Ferrando M, Melo M, Goyri E, Pellicer A, Remohi J, Meseqeur M. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertil Steril* 2010;**93**:447–454.

Bellver J, Martinez-Conejero JA, Labarta E, Alama P, Melo AM, Remohi J, Pellicer A, Horcajadas AJ. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril* 2011;**95**:2335–2341.

Carrell DT, Jones KP, Peterson CM, Aoki V, Emery RB, Campbell RB. Body mass index is inversely related to intrafollicular hCG concentrations, embryo quality and IVF outcome. *Reprod Biomed Online* 2001;**2**:109–111.

Chavarro J, Ehrlich S, Colaci D, Wright D, Toth T, Petrozza J, Hauser R. Body mass index and short term weight change in relation to treatment outcomes in women undergoing assisted reproduction. *Fertil Steril* 2012;**1**:109–116.

Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998;**6**:1502–1505.

Clark A, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, Norman R. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995;**10**:2705–2712.

Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Hum Reprod* 2003;**9**:1928–1932.

De Frene V, Verhofstadt L, Lammertyn J, Stuyver I, Buysse A, De Sutter P. Quality of Life and Body Mass Index in Overweight Adult Women with Polycystic Ovary Syndrome During a Lifestyle Modification Program. *J Obstet Gynecol Neonatal Nurs* 2015;**5**:587–599.

Department of Veterans Affairs. VA/DoD clinical practice guideline for screening and management of overweight and obesity. 2014.

Dickey RP, Taylor SN, Curole DN, Rye HP, Lu YP, Pyrzak R. Relationship of clomiphene dose and patient weight to successful treatment. *Hum Reprod* 1997;**12**:449–453.

Dietz WH, Baur LA, Hall K, Puhl RM, Taveras EM, Uauy R, Kopelman P. Management of obesity: improvement of health-care training and systems for prevention and care. *Lancet* 2015;**9986**:2521–2533.

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**6**:377–384.

Duval K, Belan M, JeanDenis F, Baillargeon J. An interdisciplinary lifestyle intervention improves clinically relevant fertility outcomes in obese infertile women-preliminary results. *Fertil Steril* 2015a;**3**:e97.

Duval K, Langlois M, Carranza-Mamane B, Pesant M, Hivert M, Poder TG, Lavoie HB, Ainmelk Y, St-Cyr Tribble D, Laredo S *et al*. The obesity-fertility protocol: a randomized controlled trial assessing clinical outcomes and costs of a transferable interdisciplinary lifestyle intervention, before and during pregnancy, in obese infertile women. *BMC Obes* 2015b;**2**:47.

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;**1**:19–25.

Farquhar C, Gillett W. Prioritising for fertility treatments?should a high BMI exclude treatment? *BJOG* 2006;**10**:1107–1109.

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Faure C, Dupont C, Baraibar MA, Ladouce R, Cedrin-Durnerin I, Wolf JP, Lévy R. In subfertile couple, abdominal fat loss in men is associated with improvement of sperm quality and pregnancy: a case-series. *PLoS ONE* 2014;**2**:e86300.

Ferlitsch K, Sator OM, Gruber MD. Body mass index, follicle stimulating hormone and their predictive value in in vitro fertilization. *J Assist Reprod Genet* 2004;**21**: 431–436.

Galletly C, Clark A, Tomlinson L, Blaney F. A group program for obese, infertile women: Weight loss and improved psychological health. *J Psychosom Obstet Gynaecol* 1996a;**2**:125–128.

Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile women following a group treatment program: An open pilot study. *Gen Hosp Psychiatry* 1996b;**3**:192–195.

Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod* 2007;**22**:414–420.

Hakonsen L, Thulstrup A, Aggerholm A, Olsen J, Bonde J, Andersen C, Bungum M, Ernst E, Hansen M, Ernst E *et al*. Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. *Reprod Health* 2011;**1**:24.

Hammiche F, Laven JSE, Twigt JM, Boellaard WPA, Steegers EAP, SteegersTheunissen RP. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. *Hum Reprod* 2012;**8**:2365–2372.

Hammoud A, Meikle A, Reis L, Gibson M, Peterson C, Carrell D. Obesity and male infertility: a practical approach. *Semin Reprod Med* 2012;**6**:486–495.

Hartz A, Barboriak P, Wong A, Katayama K, Rimm A. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes* 1979;**1**: 57–73.

Hauner H, Petzinna D, Sommerauer B, Toplak H. Effect of acarbose on weight maintenance after dietary weight loss in obese subjects. *Diabetes Obes Metab* 2001;**6**:423–427.

Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**11**:1539–1558.

Hollman M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. *Hum Reprod* 1996;**9**:1884–1891.

Homan G, Litt J, Norman RJ. The FAST study: fertility assessment and advice targeting lifestyle choices and behaviours: a pilot study. *Hum Reprod* 2012;**8**:2396–2404.

Infertility Network UK. NHS Funding for Fertility Treatment in Scotland. 2015: **October**.

Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P, on behalf of the Behavioural Weight Management Review Group. Weight change among people randomized to minimal intervention control groups in weight loss trials. *Obesity (Silver Spring)* 2016;**4**:772–780.

Källén BA. Antiobesity drugs in early pregnancy and congenital malformations in the offspring. *Obes Res Clin Pract* 2014;**8**:e571–e576.

Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. *Fertil Steril* 2010;**1**:216–220.

Karlsen K, Humaidan P, Sorensen LH, Alsbjerg B, Ravn P. Motivational interviewing: a part of the weight loss program for overweight and obese women prior to fertility treatment. *Gynecol Endocrinol* 2013;**9**:839–842.

Keltz J, Zapantis A, Jindal S, Lieman H, Santoro N, Polotsky A. Overweight men: clinical pregnancy after ART is decreased in IVF but not in ICSI cycles. *J Assist Reprod Genet* 2010;**9–10**:539–544.

Khan KS, Ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews. 2001. NHS Centre for Reviews and Dissemination.

Khaskheli M, Baloch S, Baloch AS. Infertility and weight reduction: influence and outcome. *J Coll Physicians Surg Pak* 2013;**23**:798–801.

Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, Franks S. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 1992;**1**:105–111.

Klenov V, Jungheim E. Obesity and reproductive function: a review of the evidence. *Curr Opin Obstet Gynecol* 2014;**26**:455–460.

Koning AMH. Fertility treatment in obese women. *Thesis* 2015:.

Kort J, Kim S, Lathi R. A Cohort Study to evaluate the impact of weight loss on fertility outcomes in an overweight/obese population. *Fertil Steril* 2013;**3**:S4.

Kort J, Winget C, Kim S, Lathi R. A retrospective cohort study to evaluate the impact of meaningful weight loss on fertility outcomes in an overweight population with infertility. *Fertil Steril* 2014;**5**:1400–1403.

Kumar P, Arora S. Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. *J Hum Reprod Sci* 2014;**4**:255–261.

Lazurova I, Dravecka I, Kraus V, Petrovicova J. Metformin versus sibutramine in the treatment of hyperinsulinemia in chronically anovulating women. *Bratisl Lek Listy* 2004;**5–6**:207–210.

Legro RS, Dodson WC, KrisEtherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Allison KC *et al*. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2015;**11**:4048–4058.

Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology - a systematic review. *Hum Reprod Update* 2007;**5**:433–444.

Mahoney D. Lifestyle modification intervention among infertile overweight and obese women with polycystic ovary syndrome. *J Am Assoc Nurse Pract* 2014;**6**: 301–308.

Mavropoulos JC, Yancy WS, Hepburn J, Westman EC. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab* 2005;**1**:35.

Metwally M, Cutting R, Tipton A, Skull J, Ledger LW, Li CT. Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reprod Biomed Online* 2007;**5**:532–538.

Miller PB, Forstein DA, Styles S. Effect of short-term diet and exercise on hormone levels and menses in obese, infertile women. *J Reprod Med* 2008;**5**:315–319.

Moran L, Noakes M, Clifton P, Tomlinson L, Norman R. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;**2**:812–819.

Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2011a;7:CD 007506.

Moran L, Tsagareli V, Norman R, Noakes M. Diet and IVF pilot study: Short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. *Aust N Z J Obstet Gynaecol* 2011b;**51**:455–459.

Mutsaerts MAQ, Van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WKH, Perquin DAM, Koks CAM, Van Golde R, Kaaijk EM, Schierbeek JM *et al*. Randomized trial of a lifestyle program in obese infertile women. *N Engl J Med* 2016;**20**:1942–1953.

National Clinical Guideline Centre. Obesity: Identification and management of overweight and obesity in children, young people and adults. Commissioned by the National Institute for Health and Care Excellence. 2014; 1.

National Institute for Health and Clinical Excellence. CG156 Fertility: Assessment and treatment for people with fertility problems. 2013.

North American Association for the Study of Obesity, National Heart, Blood Institute, National Institutes of Health (US), NHLBI Obesity Education Initiative. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. 2000. National Institutes of Health, National Heart, Lung, and Blood Institute, NHLBI Obesity Education Initiative, North American Association for the Study of Obesity.

Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A, Zullo F, Orio F. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. *Hum Reprod* 2010;**11**:2783–2791.

Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, Colao A, Vigorito C, Zullo F, Orio F. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum Reprod* 2008;**3**:642–650.

Qublan HS, Yannakoula EK, Al-Qudad MA, El-Uri FI. Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study. *Saudi Med J* 2007;**11**: 1694–1698.

Ramlau-Hansen H, Thulstrup M, Nohr A, Bonde P, Sørensen I, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;**6**:1634–1637.

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Salama AA, Amine EK, Salem HAE, El Fattah NKA. Anti-Inflammatory dietary combo in overweight and obese women with polycystic ovary syndrome. *Am J Med Sci* 2015;**7**:310–316.

Sallmen M, Sandler DP, Hoppin JA, Blair A, Baird DD. Reduced fertility among overweight and obese men. *Epidemiology* 2006;**5**:520–523.

Schneider G, Kirschner AM, Merkowitz R, Ertel HN. Increased estrogen production in obese men. *J Clin Endocrinol Metab* 1979;**4**:633–638.

Sermondade N, Faure C, Fezeu L, Shayeb GA, Bonde PJ, Jensen T, Van Wely M, Cao J, Martini CA, Eskandar M *et al*. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* 2013;**3**:221–231.

Shukla K, Chambial S, Dwivedi S, Misra S, Sharma P. Recent scenario of obesity and male fertility. *Andrology* 2014;**6**:809–818.

Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes* 2014a;**2**:61–68.

Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev* 2014b;**10**:839–850.

Sonmez AS, Yasar L, Savan K, Koc S, Ozcan J, Toklar A, Yazicioglu F, Akgun A, Sut N. Comparison of the effects of acarbose and metformin use on ovulation rates in clomiphene citrate-resistant polycystic ovary syndrome. *Hum Reprod* 2005;**1**: 175–179.

Styne-Gross A, Elkind-Hirsch K, Scott TR Jr. Obesity does not impact implantation rates or pregnancy outcome in women attempting conception through oocyte donation. *Fertil Steril* 2005;**83**:1629–1634.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Ovarian stimulation in assisted reproduction. 2011; 1.

Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Louis GMB. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertil Steril* 2013;**5**: 1324–1331. e1.

Thomson RL, Buckley JD, Brinkworth GD. Perceived exercise barriers are reduced and benefits are improved with lifestyle modification in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. *BMC Womens Health* 2016;**16**:14.

Thomson RL, Buckley JD, Moran LJ, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of weight loss on anti-Mullerian hormone levels in overweight and obese women with polycystic ovary syndrome and reproductive impairment. *Hum Reprod* 2009;**8**:1976–1981.

Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;**9**: 3373–3380.

Tsagareli V, Noakes M, Norman RJ. Effect of a very-low-calorie diet on in vitro fertilization outcomes. *Fertil Steril* 2006;**1**:227–229.

Turner-McGrievy GM, Davidson CR, Wingard EE, Billings DL. Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study. *Nutr Res* 2014;**6**:552–558.

Umul M, Kose S, Bilen E, Altuncu AG, Oksay T, Guney M. Effect of increasing paternal body mass index on pregnancy and live birth rates in couples undergoing intracytoplasmic sperm injection. *Andrologia* 2015;**3**:360–364.

Vahratian A, Smith YR. Should access to fertility-related services be conditional on body mass index? *Hum Reprod* 2009;**7**:1532–1537.

van Dam EW, Roelfsema F, Veldhuis JD, Hogendoorn S, Westenberg J, Helmerhorst FM, Frölich M, Krans HM, Meinders AE, Pijl H. Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome. *Am J Physiol Endocrinol Metab* 2004;**4**:E615–E620.

Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**12**:1235–1241.

Waters L, George AS, Chey T, Bauman A. Weight change in control group participants in behavioural weight loss interventions: a systematic review and meta-regression study. *BMC Med Res Methodol* 2012;**1**:120.

Wise L, Palmer J, Rosenberg L. Body size and time-to-pregnancy in black women. *Hum Reprod* 2013;**10**:2856–2864.

Wise L, Rothman K, Mikkelsen E, Sorensen H, Riis A, Hatch E. An internet-based prospective study of body size and time-to-pregnancy. *Hum Reprod* 2010;**1**:253–264.

World Health Organization. Obesity and Overweight fact sheet no 311. 2016: April 17.

Zain M, Norman R. Impact of obesity on female fertility and fertility treatment. *Womens Health (Lond)* 2008;**2**:183–194.

Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR (eds). *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific Publications, 1992;377–384.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S, International Committee for Monitoring Assisted Reproductive Technology, World Health Organization. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod* 2009;**11**:2683–2687.

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