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META-ANALYSIS ***Reproductive epidemiology***

Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women

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STUDY QUESTION: What is the impact of preconception lifestyle interventions on live birth, birth weight and pregnancy rate?

SUMMARY ANSWER: Lifestyle interventions showed benefits for weight loss and increased natural pregnancy rate, but not for live birth or birth weight.

WHAT IS KNOWN ALREADY: Evidence on the practice and content of preconception counseling and interventions is variable and limited.

STUDY DESIGN, SIZE, DURATION: Systematic review and meta-analysis (MA). Main search terms were those related to preconception lifestyle. Database searched were Ovid MEDLINE(R), EBM Reviews, PsycINFO, EMBASE and CINAHL Plus. No language restriction was placed on the published articles. The final search was performed on 10 January 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants were non-pregnant women of childbearing age intent on conceiving or their male partners. Exclusion criteria include participants with BMI < 18 kg/m^2, animal trials, hereditary disorder in one or both partners and trials focusing solely on alcohol or smoking cessation/reduction, micronutrient supplementation, or diabetes control. Anthropometric, fertility, obstetric and fetal outcomes were assessed. Bias and quality assessments were performed.

MAIN RESULTS AND THE ROLE OF CHANCE: The search returned 1802 articles and eight studies were included for analysis. Populations targeted were primarily overweight or obese subfertile women seeking reproductive assistance, with few community-based studies and none including men. MA showed greater reduction in weight ($n = 3$, $P < 0.00001$, mean difference: −3.48 kg, 95% CI: −4.29, −2.67, $I^2 = 0\%$) and BMI ($n = 2$, $P < 0.00001$, mean difference: −1.40 kg/m^2, 95% CI: −1.95, −0.84, $I^2 = 24\%$) with intervention. The only significant fertility outcome was an increased natural pregnancy rate ($n = 2$, $P = 0.003$, odds ratio: 1.87, CI: 1.24, 2.81, $I^2 = 0\%$). No differences were observed for ART adverse events, clinical pregnancy, pregnancy complications, delivery complications, live birth, premature birth, birth weight, neonatal mortality or anxiety. Risk of bias were high for three studies, moderate for three studies and low for two studies, Attrition bias was moderate or high in majority of studies.

LIMITATIONS, REASONS FOR CAUTION: Results were limited to subfertile or infertile women who were overweight or obese undergoing ART with no studies in men. The heterogeneous nature of the interventions in terms of duration and regimen means no

conclusions could be made regarding the method or components of optimal lifestyle intervention. Attrition bias itself is an important factor that could affect efficacy of interventions.

WIDER IMPLICATIONS OF THE FINDINGS: Existing preconception lifestyle interventions primarily targeted overweight and obese subfertile women undergoing ART with a focus on weight loss. It is important to note that natural conception increased with lifestyle intervention. This emphasizes the need for further research exploring optimal components of preconception lifestyle interventions in the broader population and on the optimal nature, intensity and timing of interventions.

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Introduction

The weight of reproductive aged women is increasing rapidly with 24–48% of women entering pregnancy overweight or obese (Dudenhausen *et al.*, 2015). Being overweight is associated with an increased risk of infertility and adverse maternal and fetal outcomes (Leddy *et al.*, 2008; Schummers *et al.*, 2015), which has generated an imperative to improve lifestyle preconception. Fetal development and birth outcomes are a product of both nature and nurture. The intrauterine environment is a critical component of nurture and is impacted by the health status of the mother (Martin-Gronert and Ozanne, 2006). Recommendations are, therefore, for women to enter pregnancy in the best possible health. Paternal health at conception also plays an important role in fertility and fetal outcomes. Male obesity, drug use and nutritional deficiencies can negatively affect sperm count, motility or DNA, which subsequently impacts on fertility, fetal development and live births (Frey *et al.*, 2008; Colaci *et al.*, 2012; Moragianni *et al.*, 2012). Optimizing preconception health is, therefore, of relevance to all women and men of reproductive age. However, approaches to improve lifestyle and health outcomes are poorly understood.

There are many modifiable maternal and paternal factors that can be targeted to improve health preconception. Existing research on preconception lifestyle interventions has mostly focused on assessing the effects of single preconception factors such as maternal micronutrient supplementation, smoking and alcohol (Zagre *et al.*, 2007; Yang *et al.*, 2012; Lassi *et al.*, 2014; Coles *et al.*, 2015; Zhang *et al.*, 2015), or involved specialized populations such as those with diabetes (Mahmud and Mazza, 2010; Wahabi *et al.*, 2012) or epilepsy (Winterbottom *et al.*, 2008, 2009). Very limited research has assessed the effect of multicomponent preconception lifestyle programs on optimizing weight, fertility, obstetric and fetal outcomes in the general population who are of reproductive age. Furthermore, a recent systematic review reported no randomized controlled trials (RCTs) evaluating the effectiveness of preconception interventions for improving pregnancy outcomes in overweight and obese women (Opray *et al.*, 2015).

The specific components in preconception interventions are also unclear. While there are general principles to follow for optimizing preconception nutritional intake, physical activity, weight management and medical needs (AHMAC, 2012; RACGP, 2012; Seshadri *et al.*, 2012; Warner and Frey, 2013), there is considerable variability of evidence on the practice and content of preconception counseling and interventions with no consensus or guidelines available for the broader population (RACGP, 2012; Farahi and Zolotor, 2013). Several studies have assessed knowledge improvement or behavioral changes after preconception counseling (Elsinga *et al.*, 2008), but whether those changes have any impact on pregnancy outcomes remains unclear. Moreover, there is very little research on preconception health interventions in men. In addition, attrition rates can be high in lifestyle interventions which can significantly impact on the outcome of these studies (Mutsaerts *et al.*, 2013).

Although there are clinical guidelines for preconception care, there is a knowledge gap on optimal lifestyle interventions to improve preconception health. We aimed to complete a systematic review and meta-analysis (MA) to consolidate available evidence on preconception lifestyle interventions in women and men on weight, fertility, obstetric and fetal outcomes, and assess quality of existing studies.

Materials and Methods

Selection criteria

The Participants, Intervention, Comparisons, Outcome (PICO) framework developed *a priori* was used as the protocol for this systematic review. Studies were included if participants were non-pregnant women of childbearing age intent on conceiving, either naturally or via ART or male partners of women wanting to conceive. There were no exclusions based on age or concurrent medication use as long as it was appropriately documented and consistent between groups. Studies were excluded if participants were underweight with a BMI $< 18\,kg/m^2$ to avoid studies pertaining to malnutrition and energy supplementation. Other exclusion criteria included animal trials, hereditary disorder in one or both partners, specifically those that could affect fertility, gestation and fetal outcomes (e.g. cystic fibrosis, sickle cell, thalassemia, hemophilia, fragile X and Turner syndrome); and trials focusing solely on alcohol or smoking cessation/reduction, micronutrient supplementation or diabetes control. Lifestyle interventions were defined as any modifications aiming to optimize nutritional and/or physical activity status, such as weight management, dietary changes, exercise regimens and psychological support. The comparison was those participants who received standard care/advice or no lifestyle intervention. Primary outcomes were live birth, birth weight and pregnancy rate (both from natural conception and ART). Secondary outcomes included participant quality of life, anthropometric and metabolic profile,

fertility, obstetric, fetal or child development outcomes. Detailed outcome measures are listed in Supplementary Table SI. Only RCTs were included for analysis.

Search strategy

The final search was performed on 10 January 2017 in the following electronic databases via OVID platform: Ovid MEDLINE(R), EBM Reviews, PsycINFO, EMBASE and CINAHL Plus. Clinical trials registries were searched on 23 February 2016 on Australian and New Zealand Clinical Trials registry and ClinicalTrials.gov. References of appropriate systematic reviews were searched for citations of additional relevant articles. In addition, experts in the field were asked to provide any potentially relevant studies for consideration. The search strategy was limited to English language; however, no language restriction was placed on the published articles. There were no limits on year of publication. Search terms are shown in Supplementary Table SII. The protocol was registered with PROSPERO (registration number CRD42015023952).

Article identification

Two reviewers (L.L. and B.H.) screened and performed eligibility assessment for all articles. Discrepancies were resolved through discussion and referral to a third reviewer (L.J.M.) if required to achieve consensus.

Risk of bias assessment

Two reviewers (L.L. and C.L.H.) independently assessed the risk of bias using Monash Centre for Health Research and Implementation (MCHRI) Evidence Synthesis Template for critical appraisal of a RCT (2013). Discrepancies were resolved through discussion and referral to a third reviewer (L.J.M.) if required to achieve consensus. Where there was more than one article describing a study, all articles were used to complete one risk of bias assessment on the study.

Data extraction

Two reviewers independently extracted data from relevant studies (L.L. and C.L.H.). Discrepancies were resolved through discussion and referral to a third reviewer (L.J.M.) if required to achieve consensus. Where there was more than one article describing a study, data from the most current and comprehensive article was extracted and any additional outcome data reported in additional articles were subsequently extracted.

Data synthesis

Random-effects meta-analyses (Mantel–Haenszel methods) were performed using Review Manager 5.3 (2014, The Cochrane Collaboration) if data concerning the same outcome were available from two or more studies, otherwise results were reported narratively. A second independent reviewer performed data entry checking. Endpoint data were used for MA where available, otherwise change data were used. Meta-analyses were presented as odds ratio (OR) for categorical variables or relative mean difference for continuous variables with 95% CI. I^2 was used to assess heterogeneity with significance set at >30%. Subgroup analyses according to type of intervention or number of intervention sessions or excluding high risk of bias studies were performed where possible. Qualitative data were included where MA was not possible. The PRISMA statement was followed.

Results

The search returned 1802 articles. After screening the abstracts, 88 full text articles were assessed for eligibility and from these a total of 12 articles pertaining to 8 RCTs were included for analysis (de Jong-Potjer *et al.*, 2006; Lumley and Donohue, 2006; Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Mutsaerts *et al.*, 2010, 2016; Palomba *et al.*, 2010; Moran *et al.*, 2011b; Weisman *et al.*, 2011; Sim *et al.*, 2014; Legro *et al.*, 2015; Dokras *et al.*, 2016). The PRISMA flow chart is illustrated in Fig. 1. One study was reported across three articles (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011), one of which details the study design (Downs *et al.*, 2009), with results published in other two articles (Hillemeier *et al.*, 2008; Weisman *et al.*, 2011). Another study was reported across two articles (Mutsaerts *et al.*, 2010, 2016), one being the study protocol (Mutsaerts *et al.*, 2010) with results published in the subsequent article (Mutsaerts *et al.*, 2016). A third study also published its results across two articles (Legro *et al.*, 2015; Dokras *et al.*, 2016), with one article mainly focusing on quality of life assessments (Dokras *et al.*, 2016). Meta-analyses were able to be performed for natural conception, clinical pregnancy rate, live birth rate, birth weight, pregnancy loss, pre-eclampsia, gestational diabetes, adverse ART outcomes, premature birth, neonatal mortality, participant weight and BMI. Articles that were excluded based on full text and their reasons for exclusion are summarized in Supplementary Table SIII.

Characteristics of included studies

General study characteristics of the eight included studies are summarized in Table I. Recruitment sources were Maternal and Child Health Centres (Lumley and Donohue, 2006), not for profit agencies or healthcare facilities (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011), general practitioner (GP) clinics (de Jong-Potjer *et al.*, 2006), academic health centers (Palomba *et al.*, 2010; Legro *et al.*, 2015; Dokras *et al.*, 2016), fertility facilities (Moran *et al.*, 2011b; Sim *et al.*, 2014) and University Medical Centres or General Hospitals (Mutsaerts *et al.*, 2010, 2016). Three studies were conducted in Australia (Lumley and Donohue, 2006; Moran *et al.*, 2011b; Sim *et al.*, 2014), two were in USA (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011; Legro *et al.*, 2015; Dokras *et al.*, 2016), two were in the Netherlands (de Jong-Potjer *et al.*, 2006; Mutsaerts *et al.*, 2010, 2016) and one in Italy (Palomba *et al.*, 2010). The baseline sample sizes of the included studies ranged from 38 to 2276. The total number of participants from all studies included in this systematic review was 4559. Five studies involved women with infertility undergoing ART (Mutsaerts *et al.*, 2010, 2016; Palomba *et al.*, 2010; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Dokras *et al.*, 2016).

Risk of bias of included studies

Risk of bias of included studies is summarized in Table II. Three studies had high overall risk of bias (de Jong-Potjer *et al.*, 2006; Lumley and Donohue, 2006; Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011), three studies had moderate risk of bias (Mutsaerts *et al.*, 2010, 2016; Moran *et al.*, 2011b; Legro *et al.*, 2015) and two studies had low risk of bias (Palomba *et al.*, 2010; Sim *et al.*, 2014). Most of the biases were due to poor definition of inclusion criteria, study design or comparison group specification; unclear allocation concealment or randomization method; unclear blinding or outcome reporting; moderate to high attrition rates and insufficient power. While

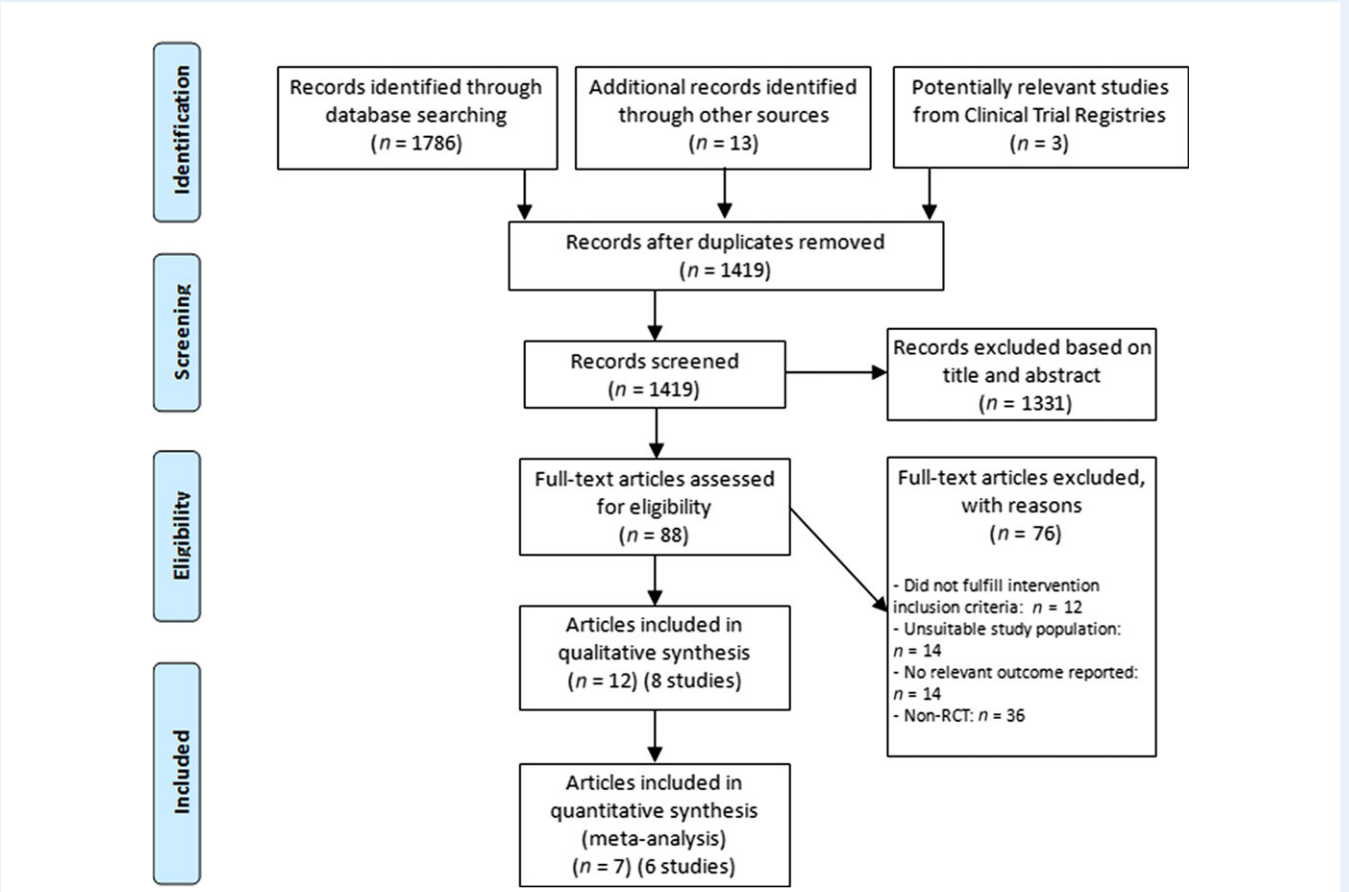

Figure 1 PRISMA flow diagram.

blinding was not performed for all studies, this is reasonable given the interactive nature of the intervention.

Population

Participants in all studies were women. The age of participants ranged between 18 and >40 years with the mean ages ranging between 24 and 34 years. The majority of participants in the studies were Caucasian (62–92%). Five studies focused on subfertile females who were overweight or obese (Mutsaerts *et al.*, 2010, 2016; Palomba *et al.*, 2010; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Dokras *et al.*, 2016). The remaining three studies involved either primiparous women (Lumley and Donohue, 2006) or women in the general community intending to become pregnant (de Jong-Potjer *et al.*, 2006; Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011). None extended into pregnancy and there were no studies that included men.

Interventions

The intervention methods were heterogeneous across studies (Table I). Three studies offered counseling sessions, two of which were individual face to face sessions delivery by either a GP (de Jong-Potjer *et al.*, 2006) or midwife (Lumley and Donohue, 2006). The third counseling intervention was group-based information and demonstration sessions on healthy preconception lifestyle (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011). The remaining five studies involved overweight subfertile women who received prescribed caloric restriction and increased physical activity with the primary goal of achieving weight loss (Mutsaerts *et al.*, 2010, 2016; Palomba *et al.*, 2010; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Dokras *et al.*, 2016). Although the degree of caloric restriction and physical activity differed in each these five studies, all were structured interventions with regular follow-ups and all involved overweight or obese women seeking ART. None of the studies offered a psychological counseling component to their intervention(s). The intervention duration ranged from single session to 6 months of intervention with multiple contact points. Intervention providers were heterogeneous in profession or otherwise not specified. Two studies utilized group intervention sessions (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011; Sim *et al.*, 2014). Two studies (Palomba *et al.*, 2010; Legro *et al.*, 2015; Dokras *et al.*, 2016) had two intervention groups and one control group. In Legro *et al.* (2015), the oral contraceptive pill (OCP) was used in the control group, but in only one of the two intervention groups. In Palomba *et al.* (2010), one of the intervention groups did not receive clomiphene. Therefore, in order to comply with our inclusion criteria, only the intervention group that received same medication as control group was included. The control groups in all studies received either baseline assessment without weight loss intervention prior to ART, or standard routine care without individual counseling sessions.

Table I Characteristic of included studies.

Study	Location/ recruitment source	Demographics (intervention versus control)	Intervention population	Control population	Intervention	Control	Attrition rate (intervention versus control)	Relevant outcome(s) assessed
Lumley and Donohue (2006)	Melbourne, Australia Maternal and Child Health Centres	Australia/New Zealand/UK/ Europe: 77.5 versus 80.2% Asia/Middle East: 19.1 versus 18% USA: 1.3 versus 0.8%	Interconception women after recent pregnancy Age <20–>40 years 1 previous pregnancy Attended Maternal and Child Health clinic with first child $n = 392$	Same as intervention $n = 394$	Midwife identified social, health or lifestyle issues and referred to specialties if required. Discussed timing and planning of next pregnancy 1 session Midwives	Home visit from midwife to discuss first pregnancy 1 session	49.5% (285/777) versus 50.9% (408/802)	Birthweight Gestational age Birth interval
Hillemeier *et al.* (2008), Weisman *et al.* (2011)	Central Pennsylvania, USA Not for profit agencies or healthcare facilities	White, non-Hispanic: 92 versus 91% Other: 8 versus 9%	Women from low-income rural communities who responded to recruitment material Age 18–35 years (mean 26.5 ± 5) English speaking Not pregnant not infertile $n = 473$	Same as intervention except mean age 24.7 ± 4.6 ($P = 0.002$) $n = 219$	Baseline risk assessment Information on general preconception health recommendations, stress and social supports. Guided physical activity, relaxation modules, healthy eating demonstrations 6 sessions (2 h each). 5 weeks duration Group facilitators	Baseline risk assessment 1 session	At 14 weeks: 46.7% (221/473) versus 49.7% (109/219) At 12 months: 53.9% (255/473) versus 61.6% (135/219)	Anthropometric measurements Pregnancy weight gain Participant weight
de Jong-Potjer *et al.* (2006)	The Netherlands GP clinics	Dutch: 94% Non-Dutch: 6%	Women identified by their GP to meet study criteria Age 18–40 years interested in preconception counseling Planning pregnancy within 1 year Not subfertile No difficult social circumstances $n = 466$	Not clearly specified $n = 1090$	GP provided preconception counseling Discussed general risk factors and individual risk factors of both partners based on risk assessment questionnaire 1 session GP	No counseling session with GP	68.1% (328/466) versus 32% (545/1703)	Anxiety score prior to counseling, after counseling and in first trimester of pregnancy
Legro *et al.* (2015), Dokras *et al.* (2016)	Philadelphia, USA Academic health centres	Hispanic: 10 versus 12.2% Caucasian: 62 versus 81.6% African American: 28 versus 14.3% Other: 10 versus 4.1%	Infertile women seeking assisted reproduction Age 18–40 years (mean 28.7) PCOS BMI 27–42 kg/m^2 Intent for ovulation induction $n = 50$	Same as intervention except mean age 29.8 years (P-value not reported) $n = 49$	Lifestyle modification involving caloric restriction with meal replacements, weight loss medication, increased physical activity to promote a 7% weight loss OCP Session number not specified. 16 weeks duration Care provider not specified	16 weeks of continuous OCP (ethinyl estradiol 20 mcg/ norethindrone acetate 1 mg) No other lifestyle intervention	14% (7/50) versus 8% (4/49)	Anthropometric measures birth weight Gestational age Ovulation rate and number of treatment cycles Pregnancy rate Pregnancy loss Live birth Fecundity Metabolic profile PCOS HRQoL questionnaire SF-36 Health related Quality of Life questionnaire PRIME-MD questionnaire

Continued

Table I *Continued*

Study	Location/ recruitment source	Demographics (intervention versus control)	Intervention population	Control population	Intervention	Control	Attrition rate (intervention versus control)	Relevant outcome(s) assessed
Moran *et al.* (2011b)	Adelaide, Australia Fertility facilities	Not reported	Overweight women with infertility seeking assisted reproduction Age 18–40 years (mean 33.4) BMI 28–45 kg/m^2 Undergoing IVF with GnRH agonist Previously had ≥1 ART cycle *n* = 21	Same as intervention except mean age 32.5 years (*P* = 0.247) *n* = 20	Nutritionally adequate reduced energy diet combined with exercise program 1 session and two follow-ups. 4 weeks duration Investigators	Standard advice on appropriate diet and lifestyle factors influencing fertility 1 session	14.3% (3/21) versus 20% (5/25)	Anthropometric measures ART outcomes Live birth
Sim *et al.* (2014)	Sydney, Australia Fertility facilities	Not reported	Overweight women with infertility seeking assisted reproduction Age 18–37 years (mean 33.4) BMI ≥ 30 kg/m^2 Intent for IVF, ICSI or cryo stored embryo transfer *n* = 27	Same as intervention except mean age 32.5 years (*P*-value not reported) *n* = 22	Weekly sessions of dietary, exercise and psychological/behavioral advice relating to weight loss and infertility Very-low energy diet for initial 6 weeks, followed by mild hypocaloric diet. Physical activity increased over 6 weeks to a daily target of 10 000 steps and maintained for another 6 weeks Fertility treatment at end of 12 weeks >6 sessions and 6 follow-ups. 12 weeks duration Fertility fellow, midwife, fertility counselor, dietitian	Advised to see GP for weight loss advice. Offered referral to weight loss service at Royal Prince Alfred Hospital If BMI ≥ 35 kg/m^2 1 session	3.7% (1/27) versus 0% (0/22)	Anthropometric measures Pregnancy rate Number of ART cycles Live birth Gestational age Pregnancy complications
Mutsaerts *et al.* (2016)	The Netherlands University Medical Centres and General Hospitals	White: 88.6 versus 86.3%	Overweight women with infertility seeking assisted reproduction Age 18–39 years (mean 29.7 ± 4.5) BMI ≥ 29 kg/m^2 ART *n* = 290	Same as intervention except mean age 29.8 ± 4.6 years (p-value not reported) *n* = 287	Decrease energy intake by 600 kcal daily Structured exercise regimen Aim to decrease weight by 5–10% 18 months of fertility treatment 6 session and 4 telephone or mail contacts. 24 weeks duration Nurse, dietitian	24 months of fertility treatment No other lifestyle intervention	3.4% (10/290) versus 1% (3/287)	Live birth Birth weight Anthropometric measures Pregnancy rate Number of ART cycles Pregnancy complications Adverse neonatal outcomes
Palomba *et al.* (2010)	Italy Academic Centres	Not reported	Overweight women with infertility and clomiphene resistance seeking assisted reproduction PCOS Age 18–35 years (mean 28.4 ± 8.31) BMI 25–34 kg/m^2 ART *n* = 32	Same as intervention except mean age 26.5 years (*P*-value not reported) *n* = 32	Structured exercise training and hypocaloric diet Clomiphene therapy after 2 weeks of intervention 18 sessions and 2 follow-ups 6 weeks duration Doctors. Others not specified	Observation for 2 weeks Clomiphene therapy after 2 weeks	0%	Anthropometric measures Ovulation rate Pregnancy rate Hormonal profile

GP, general practitioner; PCOS, polycystic ovary syndrome; OCP, oral contraceptive pill.

Table II Risk of bias of included studies.

Study	External validity	Selection bias	Performance bias	Detection bias	Attrition bias	Report bias	Confounder	Statistical bias	Overall bias
Lumley and Donohue (2006)	Moderate Inclusion/ exclusion criteria not clearly defined	Moderate Allocation not concealed	Moderate No blinding	Not reported	High	Low	Moderate No statistical comparison of baseline characteristics	Moderate Insufficiently powered	High
Hillemeier *et al.* (2008), Weisman *et al.* (2011)	Good	Moderate Method of randomization not reported Allocation not concealed	Moderate Partial blinding	Moderate Partial reporting of measurement standards	High	Moderate Not all outcomes reported	Moderate Minor differences in baseline characteristics	Moderate Inconsistencies in reporting sample size	High
de Jong-Potjer *et al.* (2006)	Poor Comparison group not clearly specified Multiple aspects of study design unclear	Moderate Allocation not concealed	Moderate No blinding	Low Used validated questionnaire	High	Moderate Not all outcomes reported	Moderate Baseline characteristics not reported	Moderate Power not reported	High
Legro *et al.* (2015), Dokras *et al.* (2016)	Good	Low	Moderate No blinding/Not reported	Moderate Not reported	Moderate	Low	Low	Moderate Insufficiently powered	Moderate
Moran *et al.* (2011b)	Good	Moderate Allocation concealment not reported	Moderate No blinding/Not reported	Moderate No reporting of measurement standards	Moderate	Low	Low	Moderate Insufficiently powered	Moderate
Sim *et al.* (2014)	Good	Moderate Partial allocation concealment	Moderate Partial blinding Intervention group underwent more fertility cycles	Moderate Partial reporting of measurement standards	Low	Moderate Not all secondary outcomes reported	Low	Low	Low
Mutsaerts *et al.* (2016)	Good	Low	Moderate No blinding Control group received longer duration of infertility treatment	Moderate No reporting of measurement standards	Low	Moderate Not all secondary outcomes reported	Low Minor differences in baseline characteristics	Moderate Insufficiently powered	Moderate
Palomba *et al.* (2010)	Good	Moderate Allocation not concealed	Moderate No blinding	Moderate Partial reporting of measurement standards	Low	Low	Low	Low	Low

Outcomes

Anthropometric outcomes

Participant's weight and BMI were assessed in six studies (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Moran *et al.*, 2011b; Weisman *et al.*, 2011; Legro *et al.*, 2015*; Sim *et al.*, 2014*; Mutsaerts *et al.*, 2016*; Palomba *et al.*, 2010) (Table III) but only those indicated by * reported results as mean ± SD were included in the MA. There were greater reductions in weight (Moran *et al.*, 2011b; Sim *et al.*, 2014; Mutsaerts *et al.*, 2016) and BMI (Moran *et al.*, 2011b; Sim *et al.*, 2014) for the intervention group (Fig. 2a and b). Non MA of endpoint weight also showed significant weight reduction (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Palomba *et al.*, 2010; Weisman *et al.*, 2011; Legro *et al.*, 2015) and BMI (Palomba *et al.*, 2010) for the intervention group. Note that in two studies, significant difference between groups was only observed at the second follow-up.

Table III Anthropometric outcomes.

Outcome	Study	Results
Participant weight(kg) and BMI(kg/m^2)	Moran *et al.* (2011b), Sim *et al.* (2014), Mutsaerts *et al.* (2016)	Weight MA: mean difference: −3.48 [95% CI:−4.29 to −2.67] $P < 0.00001$ $I^2 = 0\%$
	Moran *et al.* (2011b), Sim *et al.* (2014)	BMI MA: mean difference: −1.4 [95% CI: −1.95 to −0.84] $P < 0.00001$ $I^2 = 24\%$
	Downs *et al.* (2009), Hillemeier *et al.* (2008), Weisman *et al.* (2011)[α]	Weight 6 mo: Intervention: 72.8 [CI: 72 to 74]. Control: 74 [CI: 72.8 to 75.3] $P = 0.123$ 12 mo: Intervention: 73.5 [CI: 72.3 to 74.7]. Control: 75.5 [CI: 74.1 to 76.3] $P = 0.027$ BMI 6 mo: Intervention: 27.1 [CI: 26.7 to 27.4]. Control: 27.1 [CI: 27.1 to 28] $P = 0.110$ 12 mo: Intervention: 27.3 [CI: 26.9 to 27.7]. Control: 28 [CI: 27.5 to 28.6] $P = 0.21$
	Legro *et al.* (2015) (BMI not reported)[¶]	Intervention: −6.1 [95% CI −7 to −5.2] Control: −1.1 [95% CI: −2 to −0.3] $P < 0.0001$
	Mutsaerts *et al.* (2016)[¥]	BMI Intervention: −1.3 [−2.5 to −0.07] Control: −0.3 [−1 to −0.6]
	Palomba *et al.* (2010)t[‡]	Weigh 2 wk: Intervention: 85.9 ± 5.9. Control: 86.9 ± 6.8 6 wk: Intervention: 81.8 ± 6. Control: 86.4 ± 6.4 $P < 0.05$ BMI 2 wk: Intervention: 30.9 ± 3. Control: 32.4 ± 3.7 6 wk: Intervention: 28.4 ± 2.5. Control: 32.3 ± 3.5 $P < 0.05$

MA, meta-analysis; mo, month; [α], pregnant women excluded; [¶], mean change from baseline; [¥], median change [Interquartile range]; [‡], mean ± SD; wk, week.

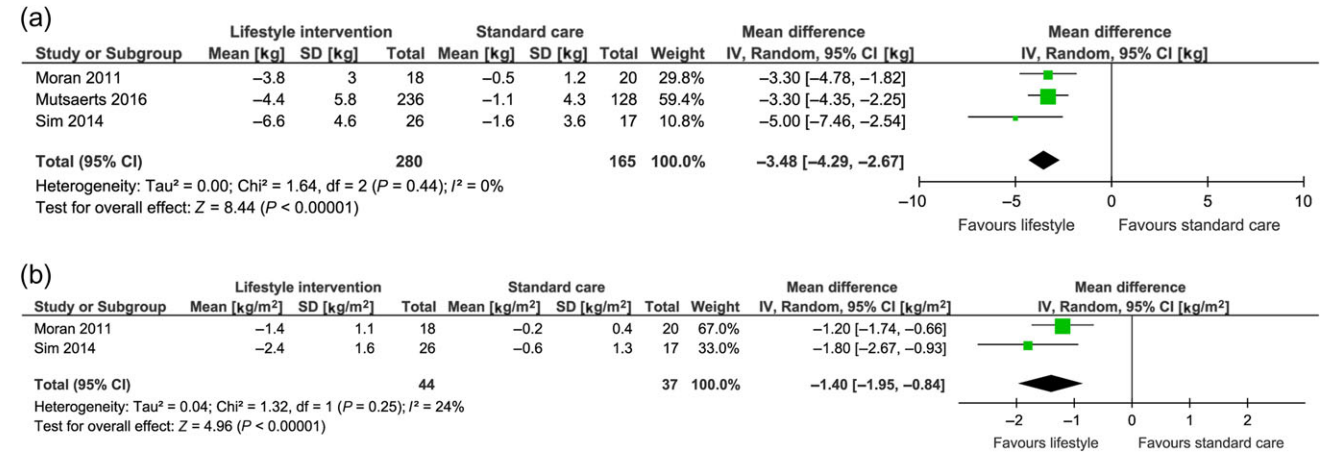

Figure 2 MA of change in participant weight (**a**) and BMI (**b**). MA, meta-analysis.

Fertility

Fertility outcomes were assessed in five studies (Table IV), all of which involved ART in subfertile overweight or obese women (Palomba *et al.*, 2010; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016). Qualitative synthesis showed a higher ovulation rate post-clomiphene treatment in women with polycystic ovary syndrome (PCOS) for the intervention group (Palomba *et al.*, 2010; Legro *et al.*, 2015) (Table IV). On MA, there were no statistically

significant differences in overall clinical pregnancy rate (which includes both natural and ART conception), between intervention and control groups (Fig. 3a). There was, however, a higher natural pregnancy rate for the intervention group (Sim *et al.*, 2014; Mutsaerts *et al.*, 2016) (Fig. 3b).

Obstetric

Obstetric outcomes were assessed in five studies (Table V) (Lumley and Donohue, 2006; Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011; Sim *et al.*, 2014; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016). MA of premature birth (Lumley and Donohue, 2006; Sim *et al.*, 2014; Mutsaerts *et al.*, 2016), pregnancy loss (Sim *et al.*, 2014; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016), pre-eclampsia and gestational diabetes (Sim *et al.*, 2014; Mutsaerts *et al.*, 2016) showed no statistically significant differences between groups. Qualitative synthesis from the only study reporting adverse ART outcomes (Mutsaerts *et al.*, 2016) showed no difference between groups. One study (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011) reported a statistically significant reduction in gestational weight gain in favor of the intervention group, which became non-significant on adjustment for pre-pregnancy obesity (BMI $\geq$ 30 kg/m^2). Only one study reported delivery complications (Mutsaerts *et al.*, 2016), which showed no statistically significant difference between groups.

Fetal

Fetal outcomes were assessed in five studies (Lumley and Donohue, 2006; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016) (Table VI). On MA, there were no statistically significant difference in live birth (Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016) (Fig. 4a), birth weight (Lumley and Donohue, 2006; Legro *et al.*, 2015; Mutsaerts *et al.*,

Table IV Fertility outcomes.

Outcome	Study	Results
Natural conception/pregnancy	Sim *et al.* (2014), Mutsaerts *et al.* (2016)	MA: OR 1.87 [95% CI: 1.24–2.81] $P = 0.003$ in favor of intervention. $I^2 = 0\%$
Clinical pregnancy	Legro *et al.* (2015), Moran *et al.* (2011b), Sim *et al.* (2014), Mutsaerts *et al.* (2016), Palomba *et al.* (2010)	MA: OR 2.1 [95% CI:–0.9–5.01] $P = 0.09$ $I^2 = 65\%$
Ovulation	Legro *et al.* (2015)$^{\beta}$	Intervention versus control: RR 1.5 [95% CI: 1.1–1.9] $P = 0.002$ in favor of intervention
	Palomba *et al.* (2010)$^{\gamma}$	Intervention versus control: RR 4 [95% CI: 1.2–12.8] $P = 0.02$ in favor of intervention

OR, odds ratio; RR, rate ratio; $^{\beta}$, number of ovulation per treatment cycle; $^{\gamma}$, number of ovulation per study participant.

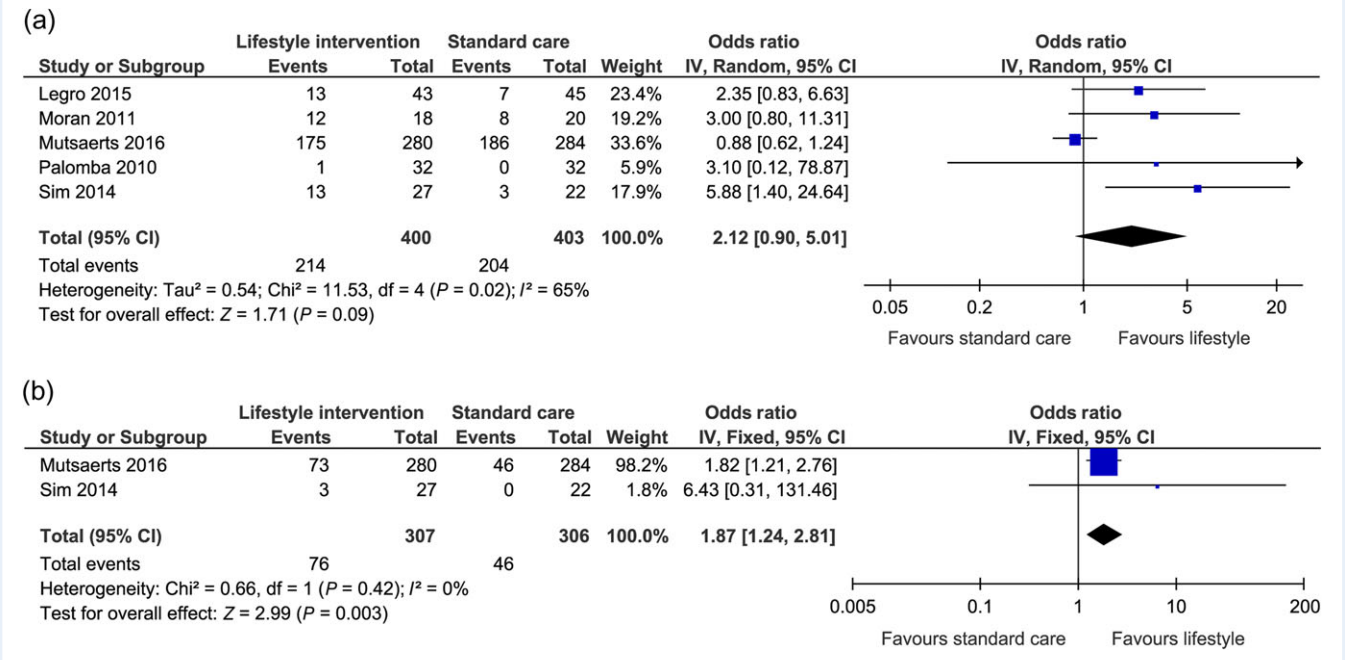

Figure 3 MA of (**a**) clinical and (**b**) natural pregnancy rates.

Table V Obstetric outcomes.

Outcome	Study	Results
Premature Birth (<37 weeks gestation)	Lumley and Donohue (2006), Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 1.06 [95% CI:0.53–2.12] $P = 0.87$ $I^2 = 40\%$
Pregnancy loss	Legro et al. (2015), Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 1.43 [95% CI:0.89–2.30] $P = 0.14$ $I^2 = 2\%$
Pre-eclampsia	Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 0.92 [95% CI: 0.39–2.13] $P = 0.84$ $I^2 = 0\%$
Gestational diabetes	Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 0.39 [95% CI: 0.05–3.24] $P = 0.39$ $I^2 = 47\%$
Adverse ART outcomes	Mutsaerts et al. (2016)	Intervention: 1.7%. Control: 1.3% (*P*-value not available)
Gestational weight gain[α]	Hillemeier et al. (2008), Weisman et al. (2011)	Intervention: 10.6 kg [95% CI: 7.49–13.74] Control: 18.8 kg [95% CI: 13.11–24.40] $P = 0.023$ in favor of intervention
Delivery complications	Mutsaerts et al. (2016)	Intervention: 22.8%. Control: 15% (*P*-value not available)

[α] $P = 0.138$ when adjusted for pre-pregnancy weight.

Table VI Fetal outcomes.

Outcome	Study	Results
Live birth	Legro et al. (2015), Moran et al. (2011b), Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 1.88 [95% CI: 0.63–5.58] $P = 0.26$ $I^2 = 79\%$
Birth weight	Lumley and Donohue (2006), Legro et al. (2015)	MA: Mean difference −197.0 g [95% CI: −501.91–107.90] $P = 0.21$ $I^2 = 56\%$
	Mutsaerts et al. (2016)[∫]	Intervention: 3312 g (IQR: 3198–3426) Control: 3341 g (IQR: 3234–3448) RR: −29 [98% CI: −185–27]
Neonatal mortality	Sim et al. (2014), Mutsaerts et al. (2016)	MA: OR 0.14 [95% CI: 0.01–1.37] $P = 0.09$ $I^2 = 0\%$
Congenital abnormalities	Mutsaerts et al. (2016)	Intervention: 3.1%. Control 3.1%. RR: 0.69 [95% CI: 0.17–2.88]

[∫], median weight; IQR, interquartile range.

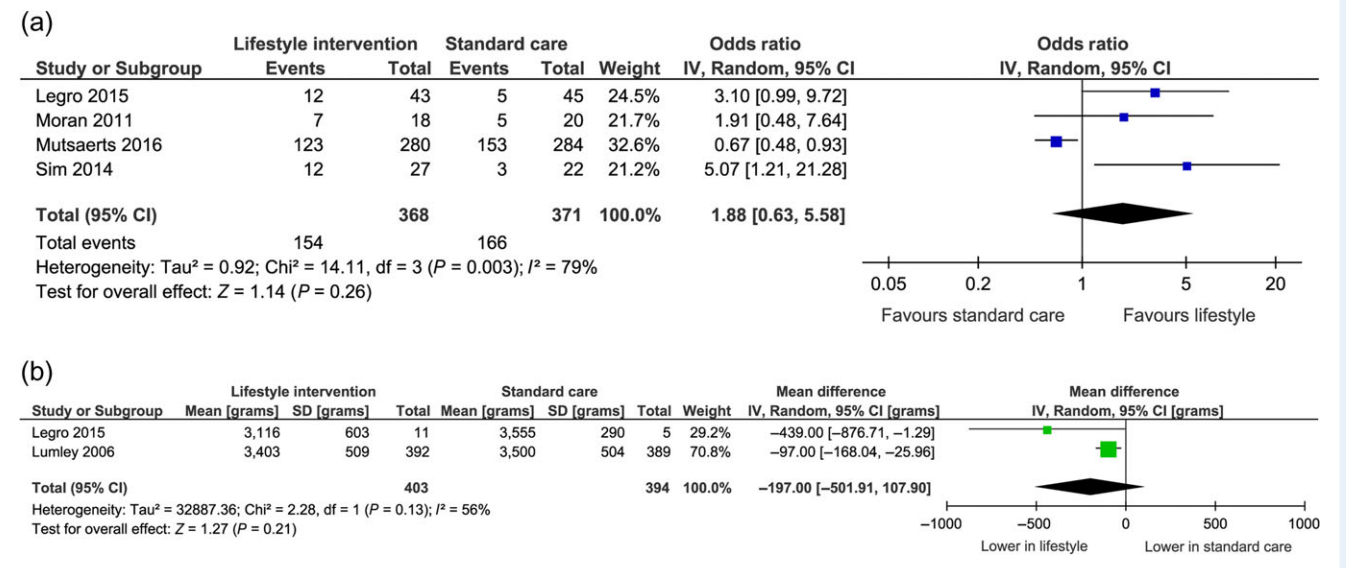

Figure 4 MA of (**a**) live birth per study participant and (**b**) birth weight.

2016) (Fig. 4b) or neonatal mortality (Sim *et al.*, 2014; Mutsaerts *et al.*, 2016) between intervention and control groups. Qualitative synthesis revealed no difference in the number of newborns that were small for gestational age (Lumley and Donohue, 2006; Mutsaerts *et al.*, 2016), defined as birth weight <10th percentile. One study (Mutsaerts *et al.*, 2016) reporting congenital abnormalities found no differences between groups.

Quality of life

Mood and quality of life were assessed in two studies (de Jong-Potjer *et al.*, 2006; Legro *et al.*, 2015; Dokras *et al.*, 2016). Qualitative synthesis showed similar Spielberger State Trait Anxiety Inventory (STAI) score between groups during first trimester (de Jong-Potjer *et al.*, 2006) (Table VII), although no significance analysis was performed between groups. Two articles used data collected from one study. In Legro *et al.* (2015), there were statistically significant improvements in multiple areas of the PCOS Health-Related Quality of Life (HRQoL) mean score in the intervention group compared to the control, namely, weight, infertility and overall physical wellbeing mean scores. In Dokras *et al.* (2016), two more questionnaires were analyzed from data collected from the original study by Legro *et al.* (2015). There were significant improvements in emotional role score of the SF-36 HRQoL questionnaire in control group compared to intervention group ($P < 0.05$). Other analyses for SF-36 HRQoL questionnaire were intra-group changes compared to baseline as summarized in Table VII. No inter-group analysis was performed for the PRIME-MD scores that assessed prevalence of anxiety and depression. However, only a small percentage of participants reported these conditions at baseline, namely, 2.3% for intervention group and 4.4% for control group.

Table VII Other outcomes.

Outcome	Study	Results
Mood	de Jong-Potjer *et al.* (2006)	Mean anxiety score during first trimester: Intervention: 37.8 [95% CI: not reported] Control: 38.5 [95% CI: 37.7–39.3] *P*-value not available
Quality of life	Legro *et al.* (2015)	PCOS HRQoL questionnaire—difference in changes of mean score between groups: Emotional: 0.2 [95% CI: −0.1–0.6] $P = 0.19$ Body hair: 0.1 [95% CI: −0.2–0.5] $P = 0.48$ Weight: 0.7 [95% CI: 0.2–1.2] $P = 0.003$ in favor of intervention Infertility: 0.5 [95% CI: 0.0–0.9] $P = 0.03$ in favor of intervention Menstrual problem: 0.2 [95% CI: −0.1–0.6] $P = 0.21$ Overall physical wellbeing: 0.7 [95% CI: 0.2–1.3] $P = 0.008$ in favor of intervention Overall emotional wellbeing: 0.2 [95% CI: −0.4–0.8] $P = 0.44$ Overall general wellbeing: 0.3 [95% CI: −0.1–0.7] $P = 0.17$
	Dokras *et al.* (2016)	SF-36 HRQoL questionnaire—Intra-group changes of mean score compared to baseline Physical component summary Intervention: 0.54 [95% CI: −1.15–2.23] Control: 1.2 [95% CI: −0.48–2.87] Mental component summary Intervention: 0.33 [95% CI: −2.09–2.75] Control: 2.4 [95% CI: 0.004–4.79] PRIME-MD questionnaire—Intra-group OR compared to baseline Depression prevalence Intervention: OR not calculated. No change in percentage Control: 0.3 [95% CI: 0.09–0.99] $P < 0.05$ Anxiety prevalence Intervention: OR not calculated Control: 0.32 [95% CI: 0.06–1.64]
Blood pressure (mmHg)	Hillemeier *et al.* (2008), Weisman *et al.* (2011)	GLM coefficients Systolic: −0.86. $P = 0.47$ Diastolic: −0.01. $P = 0.99$
	Sim *et al.* (2014)‡	Systolic Intervention: −2.2 ± 12.7 Control: 0.7 ± 11.3 $P = 0.29$ Diastolic Intervention: 1.1 ± 8.2 Control: −2.4 ± 7.5 $P = 0.2$
	Mutsaerts *et al.* (2016)¥	Systolic Intervention: 0.0 [−10, 3] Control: −3.0 [−12, 5] $P = 0.78$ Diastolic Intervention: 0.0 [−5, 4.5] Control: 0.00 [−5, 7] $P = 0.09$

Continued

Table VII *Continued*

Outcome	Study	Results
SHBG	Legro *et al.* (2015)[¶]	Intervention: 2.6 [2.15, 3.13] Control: 2.74 [2.25, 3.29] $P = 0.69$
	Palomba *et al.* (2010)[‡] (nmol/l)	Intervention: 25.37 ± 3.23 Control: 17.43 ± 3.12 $P < 0.05$
Testosterone	Legro *et al.* (2015)[¶]	Intervention: 0.41 [0.36, 0.48] Control: 0.42 [0.36, 0.48] $P = 0.9$
	Palomba *et al.* (2010)[‡] (nmol/l)	Intervention: 2.21 ± 0.67 Control: 2.51 ± 0.97 *P*-value not reported
Triglycerides	Legro *et al.* (2015)[¶]	Intervention: 1.04 [0.94, 1.16] Control: 1.19 [1.08, 1.32] $P = 0.07$
2-h post prandial glucose (mg/dl)		Intervention: 1 [95% CI: −8.3, 10.4] Control: 18.4 [95% CI: 9.2, 27.7] $P = 0.01$ in favor of intervention
2-h post OGTT insulin (uU/ml)		Intervention: 0.8 [95% CI: 0.66, 0.98] Control: 1.21 [95% CI: 1, 1.46] $P = 0.004$ in favor of intervention
Fasting glucose (mmol/l)	Palomba *et al.* (2010)[‡]	Intervention: 4.04 ± 1.74 Control: 4.02 ± 1.57 *P*-value not reported
Fasting insulin (μU/ml)		Intervention: 15.81 ± 3.95 Control: 17.91 ± 4.2 $P < 0.05$
HOMA-IR		Intervention: 1.11 ± 0.52 Control: 1.21 ± 0.62 $P < 0.05$
FSH (mIU/ml)		Intervention: 4.99 ± 3.15 Control: 4.23 ± 1.25 *P*-value not reported
LH (mIU/ml)		Intervention: 8.4 ± 3.14 Control: 8.27 ± 2.76 *P*-value not reported
Prolactin (μg/l)		Intervention: 2.63 ± 0.82 Control: 2.1 ± 0.87 *P*-value not reported
Estradiol (pmol/l)		Intervention: 116.57 ± 22.76 Control: 125.43 ± 26.6 *P*-value not reported
Progesterone (ng/ml)		Intervention: 1.07 ± 0.51 Control: 0.99 ± 0.54 *P*-value not reported
17-OHprogesterone (nmol/l)		Intervention: 0.34 ± 0.21 Control: 0.36 ± 0.26 *P*-value not reported
Androstenedione (nmol/l)		Intervention: 2.82 ± 0.78 Control: 3.18 ± 0.86 *P*-value not reported
DHEAS (μmol/l)		Intervention: 8.24 ± 0.78 Control: 8.75 ± 2.76 *P*-value not reported

F/U, follow-up; GLM, generalized linear model; SF-36 HRQoL, SF-36 health-related quality of life; [‡], mean ± SD; [¥], median [Interquartile range]; [¶], ratio of mean change from baseline [95% CI]; SHBG, sex hormone-binding globulin; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model of assessment of insulin resistance; DHEAS, dehydroepiandrosterone sulfate.

Metabolic outcomes

Blood pressure was assessed in three studies (Hillemeier *et al.*, 2008; Downs *et al.*, 2009; Weisman *et al.*, 2011; Sim *et al.*, 2014; Mutsaerts *et al.*, 2016). Non MA results showed no difference between groups. Metabolic and hormonal profiles were reported in two studies (Palomba *et al.*, 2010; Legro *et al.*, 2015). There was significant improvement in 2-h post prandial glucose, 2-h post oral glucose tolerance test insulin level, fasting insulin and insulin resistance for the intervention group compared to the control. SHBG was higher in intervention group in one study, but did not reach statistical significant in the other study. Other parameters such as triglycerides, serum glucose, fasting insulin level, gonadotrophins and sex hormones did not reach statistical significance between groups (Table VII).

Subgroup analysis

Subgroup analysis for single session intervention compared to multiple sessions was performed where possible. No differences were found in weight ($P = 0.66$, $n = 3$), BMI ($P = 0.25$, $n = 2$), clinical pregnancy ($P = 0.72$, $n = 4$) and live birth ($P = 0.68$, $n = 4$) between groups. Subgroup analyses of counseling compared to structured interventions were possible for premature birth ($P = 0.34$, $n = 3$) and birth weight ($P = 0.13$, $n = 2$) with no differences found between groups. A further sensitivity analysis was performed with exclusion of high risk of bias studies for meta-analyses of clinical pregnancy ($n = 3$), premature birth ($n = 2$), pregnancy loss ($n = 2$) and live birth ($n = 3$). There were no statistically significant differences in those outcomes after exclusion.

Discussion

We report here a systematic review and MA assessing the impact of preconception lifestyle interventions on anthropometric, fertility, obstetric, fetal, metabolic, mood and quality of life parameters in eight RCTs meeting our inclusion criteria. The populations targeted were primarily overweight infertile women seeking fertility, with a minority of studies targeting women in the general community and none targeting men. The intervention types were either single session of counseling or structured weight loss interventions. The study designs were heterogeneous and did not consistently use a multidisciplinary approach. In those trials focused on weight loss lifestyle programs in subfertile overweight or obese women, there was greater weight loss and more natural pregnancies in the intervention compared to the control groups. No differences were found between intervention and control groups in other outcomes including combined natural and ART pregnancy rate, obstetric outcomes, live birth or birth weight.

We note that five studies were structured weight loss interventions in overweight or obese subfertile women seeking ART, in keeping with the fact that obesity is associated with infertility (Jungheim *et al.*, 2013). Results of this review, therefore, are less generalizable to women who are not overweight or obese preconception and undergoing ART. In the highly selected populations reported here, both MA and individual study data showed modest weight loss (3.5 kg) with intervention compared to controls. This effect of lifestyle interventions on weight reduction is comparable to previous studies in the general population (Palomba *et al.*, 2014; Becker *et al.*, 2015). However, it also shows a paucity of literature on broader populations targeting preconception healthy lifestyle programs including those in community-based populations and in men. This is likely to reflect the lack of recognition of preconception as a lifestage and the difficulty targeting preventative program for this population outside women presenting with infertility.

Of the structured lifestyle interventions, which comprised the majority of included studies, all were narrowly focused on weight loss through caloric restriction and exercise. There was an absence of interventions directed at broader range of modifiable lifestyle factors such as behavior change and self management. Previous research demonstrates improvement in ART outcomes independent of weight loss in obese women who exercised regularly (Palomba *et al.*, 2014), and an association between poorer diet composition and infertility independent of weight changes (Chavarro *et al.*, 2007, 2008) as well as adverse effects on ongoing pregnancy (Tsagareli *et al.*, 2006; Twigt *et al.*, 2012). Therefore, future research may benefit from assessment of optimal dietary composition and physical activity levels on fertility outcomes independent of weight changes. Furthermore, while we excluded trials solely focusing on alcohol or smoking cessation/reduction, micronutrient supplementation, or diabetes control, fertility outcomes may be improved with broader multifaceted lifestyle interventions combining both diet and exercise components with other modifiable components, including micronutrient supplementation, smoking and alcohol cessation.

Regarding fertility outcomes, none of the counseling interventions addressed this area. We report no changes in infertility treatment and obstetric outcomes in the structured weight loss interventions, with the exception of improved natural pregnancy rate. Clomiphene induced ovulation rate was increased in the intervention group in association with more weight loss, consistent with previous findings (Clark *et al.*, 1995, 1998; Crosignani *et al.*, 2003). While these improvements in weight loss and ovulation did not translate to increased overall pregnancy rate (combined ART and natural), there was higher rate of natural pregnancy for the intervention group (Mutsaerts *et al.*, 2010, 2016; Moran *et al.*, 2011b; Sim *et al.*, 2014; Legro *et al.*, 2015). This is consistent with previous studies generally reporting improved ART outcomes with weight loss (Clark *et al.*, 1998; Becker *et al.*, 2015). It is, however, unclear if the increased rate of natural conception is due to the lifestyle intervention itself, or due to the fact that conventional fertility treatment was delayed in women undergoing the lifestyle intervention (van den Boogaard *et al.*, 2014). Nutritional deficiencies from caloric restriction immediately prior to ART affecting fertilization or the short duration of intervention and modest weight/BMI reduction could have impacted on separation of effects between study groups. These findings nevertheless support the benefits of modest weight loss preconception in keeping with international evidence-based guidelines (NICE guidelines, 2010), specifically, the improvement of natural pregnancy after weight loss in infertile women suggests that lifestyle changes potentially can improve fertility. However, as we did not see better outcomes for the majority of assisted infertility treatment endpoints after lifestyle interventions, our data are in agreement with a recent publication that there should be no absolute BMI threshold to allow women access to fertility treatment (Legro *et al.*, 2016).

We observed a positive effect of the intervention on quality of life outcomes from one study reported across two articles (Legro *et al.*, 2015; Dokras *et al.*, 2016). There was better overall quality of life score relating to physical wellbeing, weight and infertility and emotional role in women with PCOS, undergoing a 16-week caloric restriction and increased physical activity weight loss program, compared to control group. This is consistent with previous research reporting that weight loss is associated with improved quality of life and mood (Miller-Kovach *et al.*, 1999). This is of relevance as depression is associated with higher health risk behaviors (Verger *et al.*, 2009), poorer adherence to healthy lifestyle and adverse health outcomes (Wing *et al.*, 2002). Unfortunately, due to the small number of participants reporting history of depression or anxiety, results from the PRIME-MD questionnaire were not powered to assess the impact of lifestyle intervention on mood. One other study reported on mood (de Jong-Potjer *et al.*, 2006), a counseling intervention study which showed no increase in anxiety score as a result of preconception counseling. No study assessed the need for, and effect of, psychological support preconception, further highlighting the need for research in more diverse areas preconception. We also reported improvements in the metabolic outcomes of insulin sensitivity and glucose levels for the intervention group from one structured weight loss intervention study involving women with PCOS (Legro *et al.*, 2015), consistent with existing literature (Goodpaster *et al.*, 1999; Camastra *et al.*, 2011).

This systematic review is notable for its significant limitations, which in itself is a key finding of this original research and MA and reflects the critical need for further studies in this important field. Limitations include a lack of generalizability of the results with the majority of studies being in selected subfertile or infertile women who were overweight or obese and who were undergoing ART, with no studies in men. This review is also limited by the heterogeneous nature of the interventions with regard to duration and regimen meaning that no

conclusions could be made regarding the method or components of optimal lifestyle intervention. Numbers of studies in each meta-analysis were small, although the combined population number for included studies was moderate overall. Furthermore, only one study was adequately powered (Sim *et al.*, 2014), yet only for the outcome of clinical pregnancy. Overall, studies were only able to show a difference for anthropometric and natural pregnancy outcomes. In addition, attrition bias was moderate or high in the majority of included studies ranging from 0 to 68%. This is consistent with the broader literature on attrition rates in lifestyle intervention trials in women with PCOS (Moran *et al.*, 2011a) or the broader population (Hadziabdic *et al.*, 2015). This raises challenges for the implementation of any effective intervention into routine care. Strengths of this systematic review include the comprehensive nature of the inclusion criteria and search strategy to identify lifestyle interventions relating to either dietary, physical activity or behavioral change. This is also the first systematic review to attempt to encompass preconception lifestyle interventions in both women and men and to assess multiple domains of preconception health.

Conclusion

Despite the recognition that adverse lifestyle factors can detrimentally affect maternal, pregnancy and long-term child health outcomes, there are limited preconception lifestyle interventions aimed at improving fertility and obstetric outcomes. Existing preconception lifestyle interventions primarily targeted overweight and obese subfertile women undergoing ART. They failed to identify prevention of obesity or infertility in the broader community of preconception women and men or to explore improving diet and physical activity independent of weight loss. Importantly, the interventions that have been studied are effective for preconception weight loss in women but did not translate to better ART obstetric or fetal outcomes, except for natural pregnancy rate which was increased in intervention groups. Research is needed on optimal components of preconception lifestyle interventions, the appropriate degree and timing of weight loss in relation to conception in women and on the effect of preconception lifestyle interventions on fertility in broader community populations and in men. Moreover, future research should aim to broaden the interventions to encompass other components of preconception lifestyle such as micronutrient supplementation, smoking and alcohol cessation in conjunction with diet and exercise modifications. Adequately powered studies are needed for fertility, pregnancy and obstetric and fetal outcomes. Overall the breadth of literature in this area is limited with an imperative for greater research to inform both prevention of obesity and infertility as well as to improve pregnancy health and that of the next generation.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

L.L. contributed to the design of the study; acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content and approved the final draft for publication. C.L.H. contributed to analysis and interpretation of data and revised the article critically for important intellectual content and approved the final draft for publication. M.M. contributed to the design of the study; acquisition and analysis of data and revised the article critically for important intellectual content and approved the final draft for publication. B.H. and B.W.M. contributed to analysis of data and revised the article critically for important intellectual content and approved the final draft for publication. H.J.T. contributed to the conception and design of the study; interpretation of data; and revised the article critically for important intellectual content and approved the final draft for publication. L.J.M. contributed to the conception and design of the study; analysis and interpretation of data; and prepared, drafted and revised the article critically for important intellectual content and approved the final draft for publication.

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Conflict of interest

None declared.

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