The effectiveness of weight-loss lifestyle interventions for improving fertility in women and men with overweight or obesity and infertility: a systematic review update of evidence from randomized controlled trials.

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2021

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Key Words:

Weight-loss, infertility, obesity, systematic review, assisted reproductive technology

Running Title:

WEIGHT-LOSS TO IMPROVE FERTILITY

Acknowledgments: Melanie Bickerage and staff from the University of Aberdeen Medical Library provided assistance in the update of the search strategy. Sarah Dawson, Soniaemma Miu, Zuzanna Suchomelova and Pinja Suonpaa provided assistance scanning the titles and abstracts of articles arising from the updated search strategy. We acknowledge Dr Juan J Espinos for responding to our queries surrounding clarification and further information.

Funding: The Health Services Research Unit is funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates.

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Conflicts of interest: Dr. Maheshwari reports personal fees from Ferring and Cook, outside the submitted work. There are no other conflicts of interest to declare.

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Summary

Being overweight or obese can have a negative impact on fertility outcomes. This systematic review updates randomized controlled trial (RCT) findings on the effectiveness of weight loss interventions in reducing weight and improving reproductive outcomes of women and men with overweight or obesity and infertility. Eligible studies, published since the last review, were identified by searching databases from 20th March 2016 until 31st March 2020. RCTs involving any type of lifestyle intervention were considered. Eight RCTs were identified and aggregated with seven RCTs included in our previous review.

Meta-analyses revealed that women randomized to a combined diet and exercise intervention were more likely to become pregnant, risk ratio (RR) = 1.87 (95% CI 1.20, 2.93) and achieve a live birth RR = 2.20 (95% CI 1.23, 3.94), compared to women in control groups who received no or minimal intervention. This pattern was not replicated in trials where control groups received immediate access to assisted reproductive technology (ART). No eligible randomized trials involving men were identified. Data were largely obtained from small scale studies. Better designed, adequately powered, robust randomized trials are needed tobetter understand the effect of weight loss interventions on reproductive outcomes inboth women and men.

Abbreviations: RCT: randomized controlled trial; WHO: World Health Organization; BMI: body mass index; RR: risk ratio; CI: confidence interval;; ART: assisted reproductive technology; IVF: in vitro fertilization; IUI: intrauterine insemination; ICSI: intracytoplasmic sperm injection; VLCD: very low-calorie diet; GI: Glycemic index; Revman: Review Manager; MD: mean difference; FSH: follicle-stimulating hormone; HR: heart rate; LH: luteinizing hormone; Max HR: Maximum Heart Rate; VO2 max: Volume Oxygen Maximum; TTC: Time To Conception.

1. Introduction

Infertility, defined as 'the failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse'[1] is recognised as a global public health issue[2], estimated to affect at least 186 million people[3]. Many factors are associated with fertility problems; in women these include ovulation dysfunction, as seen in polycystic ovary syndrome (PCOS) and peritoneal and tubal factors, as seen in endometriosis[3-5]. In men these factors include low sperm count, motility and abnormal morphology[6,7]. One shared factor, found to impact fertility in both women and men, is overweight or obesity[8,9].

Almost one third of the world's population is classified as living with overweight (Body Mass Index [BMI] ≥25 to <30kg/m^2) or obesity (BMI ≥30kg/m^2)[10]. The WHO defines obesity as 'abnormal or excessive fat accumulation that may impair health' resulting from an energy imbalance between calories consumed and calories expended[11]. The negative association with reproductive outcomes has been the subject of much research[12-21]. It is predicted that increasing numbers of individuals with overweight and obesity will seek fertility treatment in the future[22,23]. In women, a higher BMI has been associated with menstrual irregularity[24-27], lower oocyte quality and quantity[28-30], longer time to conception[31-33] and higher doses of medication to stimulate ovulation[28,34,35]. In men, a higher BMI has been associated with compromised sperm production and quality[36,37]. In many countries, weight restrictions for publicly funded fertility treatment apply, with BMI determining access to such treatment[38].

Research suggests that weight loss should be considered by women with overweight or obesity to improve their chances of conceiving[13,14,39,40]. Our previous systematic review and meta-analysis investigated whether weight loss interventions, for women and men experiencing fertility problems, were successful in reducing weight and improving fertility outcomes[41]. Results obtained from randomized studies showed that weight loss interventions based on diet and exercise achieved a mean weight change of -3.98kg, 95% confidence interval, CI (-4.85,-3.12) and resulted in higher pregnancy rates compared to the control groups, risk ratio (RR) = 1.59 (95% CI 1.01, 2.50)[41]. However, we were unable to demonstrate a similar effect for live birth rate for diet and exercise, RR = 1.54 (95% CI 0.93, 2.56) or diet only interventions, RR = 6.07 (95% CI (0.34, 106.85)[41]. These results were driven by the inclusion of a large-scale trial[42]. The Lifestyle trial involved women being randomized to receive either a six-month lifestyle intervention followed by fertility treatment or immediate access to fertility treatment. The results from this well conducted, robust trial showed no significant difference in the live birth rates between the two groups at 24 months, contrasting with the findings from all small scale trials[41], raising questions surrounding the need for a lifestyle intervention over immediate access to fertility treatment[43]. Despite research suggesting that the BMI of the male partner may also play a role in fertility outcomes[19,20,36,37], the last review highlighted a lack of studies involving men[41].

Evidence from non-randomized studies in our previous review, assessed using a checklist developed for the Review Body for Interventional Procedures (ReBIP)[41], was generally found to be of poor quality and contributed little to the overall findings, therefore, this update concentrates on randomized studies which have substantially increased in number.

The aim of this systematic review update was to examine and add recent findings from RCTs of weight loss interventions to our previous systematic review to better understand their effect in reducing weight and influencing reproductive outcomes in women and men, with a BMI ≥25kg/m², experiencing fertility problems.

2. Methods

2.1 Criteria for considering studies for this review

Randomized controlled trials (RCTs) of any duration and follow up were included.

Participants in trials were women and men, clearly described as experiencing infertility, where infertility was defined as an unfulfilled desire to conceive of any duration. Studies in which participant groups met the WHO definition of overweight[11], having a group mean BMI ≥25kg/m², were included. Studies involving individuals not all actively attempting pregnancy or those with a medical condition that could cause fluctuations in weight (e.g. uncontrolled thyroid disorder, eating disorder), were excluded.

Studies included any type of dietary modification (e.g. very low-calorie diet [VLCD] using liquid meal replacements, reduced calorie or low glycemic index [GI] diets) or exercise modification (e.g. increasing daily activity or a supervised exercise) aimed at changing weight. The current update focused on non-pharmacological lifestyle interventions. Studies evaluating drug treatments and bariatric surgery were excluded.

Primary outcome measures included change in weight and live birth and clinical pregnancy rates. Live birth was defined as the complete expulsion or extraction, from a woman of a product of fertilization after 22 weeks completed gestational age, showing evidence of life[4]. Secondary outcomes included improvement in ovulation, defined by standardized tests of ovulation; menstrual cycle irregularity, with irregular cycles defined as outside the range of 26–36 days[4]; natural conception rates; conception rates following assisted reproductive technology (ART) (which includes in vitro fertilization [IVF], intrauterine insemination [IUI] and intracytoplasmic sperm injection [ICSI]), numbers of oocytes retrieved; miscarriage rates per participant and per pregnancy, with miscarriage defined as the demise of a pregnancy before the fetus reaches viability[44] and time to conception (TTC). Any potential barriers to weight loss faced by women and men with overweight or obesity, experiencing fertility problems, described in the included studies, were explored. Studies providing any of the primary or secondary outcomes were considered for inclusion.

2.2 Search methods for identification of studies

The existing search strategy from the previous systematic review was replicated and updated to identify randomized controlled trials, search dates 20th March 2016 until 31st March 2020 (Supplementary Data S2). Studies published in any language were considered. The search was conducted using the Medline, Embase and Cochrane Central Register of Controlled Trials databases. The reference list of any study meeting the inclusion criteria was also examined for any eligible studies.

2.3 Selection of studies

The titles and abstracts of search results were independently screened, against the inclusion and exclusion criteria, by one author (E.H.) and one of four colleagues. Screening of the full text was undertaken by E.H. with assistance from A.A. and D.B. Any disagreement was resolved through discussion.

2.4 Selected Studies

2.4.1 Data extraction

Using a standardized data extraction form, relevant data from new studies were identified and recorded by one author (E.H.) and verified by A.A or D.B. Information extracted included study author and institution, method of recruitment, study design, inclusion and exclusion criteria, intervention details, participants baseline characteristics, numbers of participants assessed for weight data and study outcomes. Of the newly identified studies, three authors were contacted for clarification of study results, one of whom replied[45]. One study was not published in English and required translation[46].

2.4.2 Assessment of risk of bias in included studies

The Cochrane Risk of Bias Tool Version 1[47] was used to assess risk of bias, with studies categorized as having either low, high or unclear levels of bias in a range of domains. Studies were assessed independently by two reviewers with a third reviewer available in case of disagreement.

2.4.3 Data Synthesis

Study data were summarized descriptively and reported in outcome tables. The Review Manager program (RevMan, version 5.3) was used to pool and analyze the results in a meta-analysis. Pooled results for dichotomous outcomes were presented as Risk Ratios (RR) with 95% CI and for continuous outcomes, as mean difference (MD) and 95% CI. Standard deviations (SD) and sample size were used to provide each study with a weighted value. Where not reported, SDs were calculated using available data[48].

A random effects model was used to account for the high heterogeneity generally found and expected for weight loss interventions[41]. Heterogeneity was examined using the I^2 statistic which assessed the appropriateness of pooling results of the different studies; I^2 >50% was classified as high heterogeneity. Publication bias was assessed by visual inspection of the funnel plot for outcomes where there were ten or more studies.

3. Results

3.1 Results of the search

The updated search identified eight new studies[45,46,49,50,51,52,53,54]. These eight RCTs, combined with the seven identified in our previous review[42,55,56,57,58,59,60] resulted in a total of fifteen studies eligible for inclusion in the update. The flow diagram (Fig. 1) details the overall number of citations reviewed.

3.2 Included studies

Of the fifteen studies, five were carried out in the USA[50,52,53,54,57] and two in Australia[58,60], while the others were conducted in Canada[56], Brazil[55], The Netherlands[42], Spain[45], Italy[59], Iran[46], Norway[51] and Sweden, Denmark and Iceland[49]. Four out of the fifteen were multi-center trials[42,49,51,57]. Sample sizes ranged from 12[54] to 577[42] with inclusion criteria allowing an age range from 18 to 42 years. The lengths of the interventions ranged from 4 to 48 weeks. Ten studies evaluated diet and exercise combined[42,45,50,53,54,56,57,58,59,60], two studies examined the effects of diet alone[49,55], two focused on exercise alone[46,51] and another examined the use of a pedometer added to dietary and exercise counselling[52]. Characteristics of the studies are displayed in Supplementary Data S1.

Where reported, duration of infertility in the intervention groups ranged from 22 months[42] to 5.6 years[45]. No significant differences in duration of infertility between the intervention and control groups was reported. Studies included women referred to receive fertility treatment[51,55,60], women receiving fertility treatment[49,58] or both [45,52]. Women with PCOS and infertility were the focus of some studies[46,50,52,57,59] and were included in others[49,53,55,60]. Studies also included women who were anovulatory[42,54] and those experiencing ovulatory dysfunction and seeking fertility[53,60].

3.3 Risk of bias in included RCTs

The risk of bias assessment revealed expected variability in the quality of the included studies (Supplementary Data S3). Due to the nature of the research, blinding was not possible for participants and personnel, therefore, all included RCTs were identified as being at high risk of performance bias. Four of the fifteen RCTs achieved five out of seven domains of low risk of bias and seven studies had only one domain indicating a high risk of bias. Interpretation of the funnel plots was limited due to the small number of studies included in this review, however, no gross asymmetry was observed for change in weight, pregnancy rate and live birth rate (Supplementary Data S4).

3.4 Types of Diet

A number of different dietary interventions were utilized within the included trials, ranging from very low-calorie diets (VLCDs) involving liquid meal replacements to classic reduced calorie diets, to diets involving the consumption of low GI or high protein foods or eating in line with government recommendations.

VLCDs reduced caloric intake to as low as 400 kcal/day for a period of 6-12 weeks and were followed by a period of gradual food re-introduction, usually under the guidance of a dietitian[49,53,54,60]. Three VLCD interventions resulted in the greatest reduction in weight[49,53,54], while the other resulted in a reduction comparable to less restrictive diets[60]. Three included an exercise component which may have played a role in weight reduction[53,54,60]. However, the intervention involving VLCD alone also achieved a large reduction in weight in the intervention group compared to controls[49].

The remaining RCTs involved reduced-calorie personalized dietary plans, provided by dietitians, tailored to cut the caloric intake of participants by 500-1000kcal/ day[42,45,50,54,56,57,58,59]. Diets recommended included consumption of low GI[50,55] and/ or high protein foods[58,59], strictly three meals and two snacks per day[45] or a diet in line with national guidelines[42,56]. All but one intervention included an exercise component[55]. Weight reduction from these food-based diets was comparable to that achieved by VLCDs in two studies[45,50]. Even where weight loss was lower [42,57,58,59], there was still a substantial reduction in weight in the intervention groups compared to controls. A summary of the diets in the included studies can be found in Supplementary Data S1

Only one study reported dietary changes achieved by participants during the intervention[55]. Women randomized to the diet only intervention reduced their overall caloric intake more (reported $p = 0.001$) and consumed higher levels of protein (reported $p = 0.03$) and fiber (reported $p = 0.02$) than women in the control group[55] (Table 1).

3.5 Types of Exercise

The exercise component of the included interventions mainly consisted of a gradual increase in physical activity with most interventions encouraging participants to achieve 150-200 minutes of aerobic exercise a week[42,45,46,50,52,54,56,57,58605]. This was achieved through walking[52,54,56,57,60], a combination of walking plus moderate physical activity[42], walking plus conditioning exercises[58] and structured aerobic exercise sessions[45,46,59].

One RCT encouraged participants to gradually increase their exercise levels and intensity to achieve 280 minutes of moderate activity per week, almost double the number of minutes compared to other interventions; however, whether participants in the intervention group achieved this level of activity is unclear[53].

High intensity interval training was prescribed in one study examining the impact of exercise alone on reproductive outcomes[51]. A summary of the exercise prescribed in the included studies can be found in Supplementary Data S1.

The effect of the interventions on the actual exercise behavior of participants varied. Results ranged from high levels of compliance with prescribed exercise programs[51] and higher activity levels performed by those receiving the intervention compared to the control group (reported $p = <0.05$)[59] to only 30% of participants achieving their goal of increasing their activity levels[52]. (Table 1).

3.6 Types of Control Group

Generally, the control groups received no[46,49,54,55,57,59] or minimal[51,58,60] intervention. Minimal interventions included standard care consisting of advice on dietary and lifestyle factors at one session with no active follow up[58], standard advice plus the same weekly printed materials as the intervention group[60] or advice from hospital staff on physical activity alongside encouragement to adhere to current Norwegian dietary recommendations[51]. In four studies, participants in the control group received immediate access to ART[42,45,49,56]. In a single study, participants received standard advice on diet and exercise from a dietitian[53] and in another they were provided with counselling around their exercise and nutritional goals[52]. The meta-analysis is structured to reflect the differences in control groups as well as intervention type.

3.7 Primary Outcomes

3.7.1 Change in Weight

Overall, participants randomized to receive lifestyle interventions achieved greater reduction in weight compared to those who received no or minimal intervention or immediate access to ART in the control groups MD = -5.24kg (95% CI -7.14, -3.35) (Fig. 2).

Participants randomized to diet and exercise interventions experienced greater weight reduction compared to participants in the no or minimal intervention control groups[50,54,55,58,59,60] MD = -4.66kg (95% CI -6.03, -3.30) and compared to those receiving immediate access to ART[42,45] MD = -4.16kg (95% CI -6.87, -1.44). Results from a single study suggest VLCD and exercise to be advantageous over standard diet and exercise[53] MD = -9.00kg (95% CI -15.50, -2.50). Similarly, diet only interventions were found to be effective at reducing weight compared to no or minimal intervention[55] MD = -5.23kg (95% CI -7.42, -3.04) and immediate access to ART[49] MD = -10.29kg (95% CI -11.42, -9.16). In contrast, there was no real advantage of exercise only interventions for weight reduction compared to controls[46,51] MD = -0.49kg (95% CI -4.36, 3.39). We explored the effect sizes of all diet and exercise interventions versus all diet only interventions and found no significant difference in terms of weight reduction, however, both showed better effects than exercise alone ($p \leq 0.05$). (Supplementary Data S5).

Random effects meta-analysis revealed high heterogeneity $I^2 = 91.9\%$, suggesting it may not be appropriate to compare the different studies in this way.

3.7.2 Live Birth Rates

Overall, there were more live births in the intervention groups (42.9%) than in the control groups (39.5%), RR = 1.46 (95% CI 1.04, 2.04) (Fig.3). The results showed an effect from diet and exercise compared no or minimal intervention RR = 2.20 (95% CI 1.23, 3.94)[57,58,60] and compared to immediate access to ART in two small studies[45,56]. In contrast, there was no effect from diet and exercise compared to immediate access to ART in the larger study by Mutsaerts et al[42]. Similarly, no effect was found from a VLCD compared to standard diet and exercise[53] or from diet alone versus no or minimal intervention[55] or immediate access to ART[49].

3.7.3 Clinical Pregnancy Rates

Women randomized to receive a reduced calorie diet and exercise intervention were more likely to become pregnant when compared to those receiving no or minimal intervention[57,58,59,60] RR = 1.87 (95% CI 1.20, 2.93) but this was not replicated when compared to those receiving immediate access to ART RR = 1.43[42,45,56] (95% CI 0.83, 2.48) (Fig 4). Similarly, no advantage was found for interventions involving a VLCD over standard diet and exercise[53] RR = 7.00 (95% CI 0.43, 114.70), diet only versus no or minimal intervention[55] RR = 6.07 (95% CI 0.34, 106.85), diet only versus immediate access to ART[49] RR = 1.11 (95% CI 0.80, 1.53) exercise only[51] RR = 1.13 (95% CI 0.41, 3.08) or the use of a pedometer alongside diet and exercise counselling[52] RR = 1.47 (95% CI 0.43, 5.01), compared to control groups, but confidence intervals were wide.

3.8 Secondary Outcomes

3.8.1 Improvement in ovulation

Results suggested an improvement in ovulation rates following diet and exercise interventions compared to no or minimal intervention with 40.5% of participants achieving ovulation in the intervention groups compared to 8.3% in the controls[54,59] RR = 4.24 (95% CI 1.45, 12.39) (Fig. 5). These findings were not replicated in a small study examining the effect of a very low-calorie diet and exercise compared to standard diet and exercise[53] RR = 7.00 (95% CI 0.43, 114.70) or in the study which added pedometer use to diet and exercise counselling[52] RR = 4.40 (95% CI 0.59, 33.07).

3.8.2 Menstrual Cycle Irregularity

None of the newly identified studies explored improvements in menstrual cycle irregularity. One study[59], included in the previous review, showed participants randomized to receive diet and exercise experienced an improvement in menstrual cycle regularity compared to the control group RR = 3.67 (95% CI 1.13, 11.92) (Fig. 6).

3.8.3 Natural Conception Rates

Overall, women in the intervention groups were more likely to experience a natural conception compared to controls RR = 2.25 (95% CI 1.42, 3.59) (Fig. 7). The diet only intervention of Einarsson and colleagues[49] was advantageous in increasing natural conception rates compared to immediate access to ART RR = 3.92 (95% CI 1.34, 11.48). Interventions involving both diet and exercise showed no advantage compared to immediate access to ART[42,56] RR = 2.20 (95% CI 0.98, 4.93). Similarly, no significant advantage was found for interventions involving diet and exercise[50] and exercise only[51] compared to control groups receiving no or minimal intervention.

3.8.4 Conception Rates following Assisted Reproductive Technology

Lifestyle interventions involving diet and exercise[42,45,56,60], diet alone[49] or exercise alone[51] had no impact on conception rates following ART compared to controls (Fig. 8). Overall, 16.0% conceived through ART following a lifestyle intervention compared to 17.6% in the control groups RR = 1.05 (95% CI 0.69, 1.59).

3.8.5 Number of oocytes retrieved

Only two RCTs examined oocyte retrieval rates (Fig. 9). The aggregated data indicates no influence of diet alone on the number of oocytes retrieved compared to no or minimal intervention[55] or immediate access to ART[49] MD = -1.62 (95% CI -4.95, 1.35).

3.8.6 Miscarriage Rates per Participant

Lifestyle interventions including both diet and exercise were not associated with an increased risk of miscarriage per participant compared to no or minimal intervention[57,60] RR = 0.95 (95% CI 0.79, 1.15) or immediate access to ART control groups[42,45] RR = 0.95 (95% CI 0.90, 1.01) (Fig.10). Similar results were found for interventions involving diet alone[49] RR = 0.98 (95% CI 0.94, 1.03).

3.8.7 Miscarriage Rates per Pregnancy

In line with miscarriages per participant, the intervention involving diet alone was not associated with an increase in miscarriage rates per pregnancy compared to immediate access to ART[49], RR = 0.96 (95% CI 0.85, 1.09) (Fig. 11). Interventions involving diet and exercise showed no difference compared to no or minimal intervention[57,60] RR = 1.22 (95% CI 0.75, 1.99) or immediate access to ART controls[42,45] overall RR = 0.92 (95% CI 0.82, 1.03). However, results from one study[42] revealed a trend toward an increase in miscarriage rates per pregnancy in the intervention group compared to the control group RR = 0.90 (95% CI 0.82, 0.99).

3.8.8 Time to conception

No newly identified studies explored TTC. One study[42], included in the previous review, reported the median TTC, resulting in a live birth, was 7.2 months, interquartile range (IQR) 2.6,12.0, in those randomized to receive a diet and exercise intervention, compared to 5.2, IQR 2.4, 10.1, in the control group.

3.9 Barriers to weight loss

Reporting of barriers to weight loss was not the main focus of any of the studies selected for inclusion in the systematic review update. However, various issues, that could be considered barriers preventing weight reduction, were discussed by authors in six studies[49,50,51.52,53,57]. Ways to overcome these barriers were considered in two studies[50,60]. Details are summarized in Table 1.

Although health care professionals may be aware of the risks surrounding obesity during pregnancy, it is argued that insufficient training in obesity management and a lack of knowledge in ways to help their patients to reduce their weight safely may discourage them from discussing weight loss with their patients[53]. Beliefs held by women seeking pregnancy may make them reluctant to delay fertility treatment and undertake a period of weight loss[53] (Table 1). Such barriers could potentially explain recruitment issues reported by a larger-scale study where a high proportion of eligible patients declined to participate and be randomised[49].

Social factors, including the safety of the neighborhood and long working hours, were identified as potential barriers preventing participants achieving their exercise goals in studies where participants were provided with a pedometer[52] (Table 1).

One study, involving high intensity interval training, aimed to recruit 140 participants over 5 years, however, after four years, recruitment was terminated as only 18 women agreed to take part[51]. Although adherence to the program was high, the very low recruitment rate suggests this type of intervention may not be appealing to most women of reproductive age.

Legro and colleagues suggested that evidence from larger, more robust studies coupled with patient and physician education is needed to increase the willingness of women to defer fertility treatment and undertake a preconception lifestyle programme[57]. Hoeger and colleagues suggested incentives, which build over time, could be used in trials to boost recruitment and encourage long term retention[50], however, the type of incentive that could be useful within this population group was not specified. Furthermore, there was no discussion surrounding the practicality of including incentives; it may not be possible to provide these outside the context of the randomized trial. Sim and colleagues suggested that group meetings may have been the reason for enhanced retention observed during their study[60], however, results from other trials included in the current review do not appear to provide support for this suggestion. While one study involving group meetings reported no drop out[59], the others reported rates of 20%[60] and 39%[50], comparable to[42,51,53,55] or higher than[49,57,58] drop-out rates in studies where participants were seen individually.

Changes to diet and exercise were not widely reported, however, studies suggest that participants receiving a dietary intervention significantly reduced their caloric intake[55] and increased their physical activity levels[59] compared to those in the control groups (Table 1).

All trials included in the review update examined the influence of diet and/or exercise interventions on the weight and reproductive outcomes of women only. There were no lifestyle trials involving male partners of infertile couples and there were no trials involving couples.

4. Discussion

This systematic review update focuses on randomized studies aimed at reducing the weight of women and men experiencing infertility, adding eight new trials to the seven included in the previous review. The updated review explores the effect of a variety of lifestyle interventions on reproductive outcomes against different types of control conditions. Participants randomized to receive lifestyle interventions experienced weight loss regardless of intervention type, however, greater reductions were seen in those receiving diet and exercise and diet alone interventions compared to those randomized to exercise only. Overall, results suggest that lifestyle interventions can be beneficial for increasing live birth and clinical pregnancy rates. However, while combined diet and exercise interventions compared to no or minimal intervention control groups show significant increases in clinical pregnancy and live birth rates, this is not replicated in studies where control groups receive immediate access to ART.

The greatest reduction in weight was achieved in interventions utilizing VLCDs, however, some less restrictive, food-based plans resulted in comparable weight loss[45,50,55]. The inclusion of exercise alongside the VLCD appeared to further enhance weight reduction[53,54]. However, studies demonstrating this effect included participants with the highest starting weights and consisted of the smallest sample sizes and therefore, results should be treated with caution. Although diet alone resulted in significant weight reduction, research suggests that it may not be enough on its own for weight maintenance[61,62]. Overall, the systematic review update suggests lifestyle interventions are advantageous in increasing live birth and clinical pregnancy rates. However, this finding is driven by the results of small-scale studies. Neither of the larger trials found any evidence of a difference in pregnancy or live birth rates between the intervention and control groups when immediate access to ART was offered to the controls[42,49]. Greater reductions in weight did not result in higher chances of pregnancy and pregnancy rates in studies achieving similar reductions in weight varied[57,60]. Overall, miscarriage rates per pregnancy and per participant demonstrate that lifestyle interventions were not associated with an increased risk of miscarriage.

Although an increase in natural pregnancies was observed in the intervention group of both the larger-scale trials, overall results were driven by the study design. In both, the control group received immediate access to ART whereas the intervention group participated in the weight loss intervention before receiving ART, meaning they had a longer time to attempt to conceive naturally[42,43,49]. Large scale trials, where the control group waits the length of the intervention before accessing ART, could help clarify whether the prolonged period for attempting pregnancy or the weight loss itself, improves natural conception rates. No intervention showed an advantage in relation to increasing ART conception rates compared to controls, contrasting with existing research which suggests that reducing weight increases the chances of ART being successful[8,25,32,63]. This leads to questions surrounding the importance of weight reduction prior to ART treatment [43,64,65]. However, given the weight of participants in the included studies at baseline and the reported weight reductions, it is plausible that participants failed to reduce their weight and obtain a BMI<25kg/m^2. Achieving a healthy weight should remain a priority for women seeking pregnancy to reduce any risk of gestational diabetes, preterm birth, preeclampsia, macrosomia, higher rates of caesarean section as well as long term health implications for the child and mother[66-69].

Ovulation rates were improved in the intervention groups compared to controls, however, results did not reveal an optimal amount of weight loss required for this improvement. While the study eliciting the greatest reduction in weight resulted in the greatest increase in ovulation rate[54], other studies with varying amounts of weight loss saw comparable improvements[52,53,59].

Unfortunately, there were insufficient studies within each category to conduct sub-group analyses by starting BMI in relation to the primary and secondary outcomes. Staring BMI may be an important determinant which should be explored in relation to the various outcomes in the future when sufficient data allows.

Potential barriers to achieving weight loss need to be fully considered and addressed when developing interventions to ensure participants can engage fully. For example, when asking participants to increase their step count, intervention developers must ensure there are safe places for walking or alternatives such as home equipment or access to gym or sport facilities. Additionally, the intervention must be appealing to potential participants. While incentives that build over the duration of a trial might prove useful in enhancing recruitment and retention to trials[50], we need to outline what such incentives look like and assess whether it would be feasible to use such incentives outside the trials themselves.

Strengths of the review update include the addition of eight further RCTs. The cohort and non-randomized studies included in our previous review were found to contribute little to the overall findings, with few of even moderate quality[41]. While all studies included in the current review scored high on bias relating to issues surrounding blinding of participants and personnel, this was unavoidable due to the nature of the intervention where participants and clinicians or researchers delivering the intervention could not be blinded to group allocation. There were very few studies with high risk of bias in any other domains (Supplementary Data, S2).

Unfortunately, there were no RCTs looking at the effects of weight loss on fertility outcomes in men. The previous review included two non-randomized studies which suggested weight loss could help improve sperm concentration, motility and morphology[70,71] and recent systematic review evidence, from cohort and cross-sectional studies, suggests maintaining a healthy weight is important for sperm quality[27]. All trials included in our review explored the effect of weight loss of the woman seeking pregnancy alone; the weight of their partner was not considered. The presence of a male partner with overweight or obesity, with the potential for compromised sperm quality, motility and morphology could have influenced outcomes in some couples.

Couples often have the same dietary patterns, physical activity levels and share patterns of sedentary behavior which can lead to concordance in weight and BMI[73,74,75] and therefore, overweight or obesity may be an issue for both members of the couple. Where necessary, this should be acknowledged and studies or interventions aimed at improving fertility in couples actively seeking pregnancy, developed accordingly. In the fertility context, unlike any other, couples attend together for appointments and support each other during treatment[76]. A couple-based approach to weight loss would be feasible and acceptable in this context.

Overall, the results of this systematic review update suggest that, in women, weight reduction following a lifestyle intervention increases the chances of pregnancy and live birth. However, these results are driven by smaller scale studies, which evidence from larger trials providing immediate access to ART fertility services does not support. Further evidence from robust, well designed, large-scale trials is required and where necessary, future studies should consider involving both partners to fully explore the impact of weight reduction on fertility outcomes.

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Table 1: Changes to diet or physical activity, barriers to weight loss and potential enablers to boost participation in weight loss studies

Study	Change to diet or physical activity	Barrier identified	Enabler proposed
Diet & Exercise			
Hoeger et al., 2004[50]			Incentives, which build throughout the length of the trial
Palomba et al., 2010[59]	Leisure time physical activity levels increased in the intervention group compared to the control group (p = <0.05)		
Rothberg et al., 2016[53]		Women seeking pregnancy believe: Weight loss will take too long A weight loss attempt will be unsuccessful The risks of obesity in pregnancy were small	
Sim et al., 2014[60]			The use of a group-based approach as opposed to individual treatment program
Diet Alone			
Becker et al., 2015[55]	Overall caloric intake was reduced in the intervention group compared to the control group (p = 0.001). Participants in the intervention group consumed more protein (p = 0.03) and fibre (p = 0.002) than those in the control group.		
Exercise Alone			
Kiel et al., 2017[51]	On average, participants in the intervention group completed 85% of the prescribed exercise sessions. In the 4x4 minute sessions, participants worked at 92% maximum heart rate (HR) and 92% maximum HR in the 10×1 min sessions. The		

Study	Change to diet or physical activity	Barrier identified	Enabler proposed
	activity levels of participants in the control group was not reported.		
Nagelberg et al., 2016[52]	Many participants (40%) in the pedometer group increased their baseline steps by 21% weekly. Three out of 10 participants achieved the step count goal of a 50% increase in steps weekly, to a maximum of 10,000 steps per day. The activity levels of participants in the control group were not reported. Dietary changes were not reported for either the intervention or control groups.	Potential barriers: Neighborhood safety Long working hours The cost and accessibility of fresh produce	