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The effect of physical activity on reproductive health outcomes in young women: a systematic review and meta-analysis

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BACKGROUND: In the context of increasing rates of overweight and obesity in young adult women, and the increasing numbers of women seeking help for fertility problems, it is important to understand whether physical activity (PA) could help with management of reproductive health problems, with or without weight loss.

OBJECTIVE AND RATIONALE: The primary aim of this systematic review and meta-analysis was to assess the effects of PA on selected reproductive health outcomes in young adult women, in order to inform best practice advice for women in terms of promoting fertility and reproductive health in young adulthood.

SEARCH METHODS: An electronic search of PubMed, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Web of Science, SportDiscus, and Cochrane was performed for studies published between January 2000 and May 2018. Keywords and Medical Subject Headings terms related to PA, reproductive health, and weight gain were used. Studies were selected if they were intervention studies, if PA was delivered as part of an intervention to pre-menopausal women, and if any reproductive health outcome was reported. Quality analysis was performed using the Tool for the assEssment of Study qualiTy and reporting in EXercise.

OUTCOMES: Eighteen studies, with a mix of four types of study design (4 randomized controlled trials (RCTs), 11 randomized comparison trials, 2 non-randomized comparison trials, and 1 single-arm clinical trial), were identified. Comparisons included fertility treatment (four studies) and common treatments for women with polycystic ovary syndrome (PCOS) symptoms (nine studies). Pooled analysis of data from three of the four studies with a control group showed higher pregnancy [risk ratio (RR) 2.10, 95% CI (1.32, 3.35); three studies] and live birth [RR 2.11, 95% CI (1.02, 4.39); two studies] rates in the intervention groups compared with non-therapy controls. Aggregated data from the fertility treatment comparative studies (i.e. those that compared PA with standard fertility treatment such as clomiphene, gonadotrophins, and/or IVF) showed no significant intervention differences: RR 1.46, 95% CI (0.87, 2.45) for clinical pregnancy (four studies) and RR 1.09, 95% CI (0.56, 2.12) for live births (two studies). Pooled analysis from the comparison trials that used pharmaceutical or dietary treatment for PCOS as comparison showed higher pregnancy rates [RR 1.59, 95% CI (1.06, 2.38); five studies] and live birth rates [RR 2.45, 95% CI (1.24, 4.83); two observations] in the PA intervention groups than in the comparison groups. Analysis of other outcomes, such as ovulation rates, menstrual regularity, and conception rates, showed no differences between the PA intervention and comparison groups.

WIDER IMPLICATIONS: There is emerging evidence from RCT that PA may improve pregnancy rates in women with reproductive health problems. Comparative studies indicate that PA intervention may be as effective as other commonly used clinical intervention strategies for improving reproductive health outcomes. While the type, intensity, frequency, and duration of optimal PA intervention, and the role of PA independent of weight loss, remain unclear, these preliminary findings suggest that PA may be an affordable and feasible alternative or complementary therapy to fertility treatments.

Key words: systematic review / meta-analysis / physical activity / exercise / reproductive health / ovulation / menstrual cycle / conception / live births / pregnancy

Introduction

It is well known that physical activity (PA) is beneficial for disease prevention and is associated with reductions in the risk of a large number of diseases and conditions, including cardiovascular disease, type 2 diabetes, and breast and colon cancers, among others (2018 Physical Activity Guidelines Advisory Committee, 2018). Relationships between PA (or physical inactivity) and reproductive health outcomes are, however, less well understood. The recently released '2018 Physical Activity Guidelines Advisory Committee Scientific Report' states that, in addition to disease-prevention benefits, women who are more physically active are less likely to gain excessive weight during pregnancy. This is coupled with reduced risks of developing gestational diabetes and post-partum depression (2018 Physical Activity Guidelines Advisory Committee, 2018).

These observations highlight the complex interplay between PA and weight gain in young adult women. Observational data from the Australian Longitudinal Study on Women's Health suggest that, when women are in their 20s and 30s, levels of PA tend to decline slightly, fluctuating with life events such as getting married and having a baby. Between the ages of 18–23 years and 31–36 years, only 18% of this young adult cohort maintained adequate levels of PA at five consecutive three-yearly surveys (Dobson *et al*., 2012). Over the same period, the proportion of women whose BMI was in the overweight or obese categories increased from 21% to 45% (Dobson *et al*., 2012). This is important, because reproductive problems, such as infertility, are known to be more prevalent in overweight and obese women (Dağ and Dilbaz, 2015), and research has shown that low levels of leisure time PA may increase the risk of menstrual irregularities (Gudmundsdottir *et al*., 2014), especially if coupled with overweight (Dağ and Dilbaz, 2015) or obesity (Hartz *et al*., 1979; Sim *et al*., 2014a; Mutsaerts *et al*., 2016).

Research with athletes suggests that high levels of PA are associated with menstrual irregularities and subsequent potential infertility (Warren and Perlroth, 2001; Torstveit and Sundgot-Borgen, 2005; Gifford *et al*., 2017). It is likely that these reproductive health problems are caused by a complex interplay of exercise-induced neuroendocrine mechanisms, whereby acute increases in ovarian hormone levels during exercise perturb hypothalamic neuroendocrine pathways, resulting in chronically low levels of circulating estradiol and reduced ovarian stimulation (De Crée, 1998). These changes are most notable when there is negative energy balance, as observed in many athletes (Warren and Perlroth, 2001; Williams *et al*., 2015). However, in the general population, especially in mid-high-income countries, many young adult women are in positive energy balance and do not do excessive amounts of exercise.

In the non-athlete context, most research into PA and fertility has focused on overweight and obese women with ovulatory disorders such as polycystic ovary syndrome (PCOS). This condition is underpinned by weight-independent insulin resistance and is associated with reproductive and cardiovascular complications (Harrison *et al*., 2010). Studies that have compared diet and exercise interventions in women

with PCOS have shown that exercise has a more lasting effect on reducing insulin resistance (Hutchison et al., 2011) and a greater effect on restoring ovulation (Palomba et al., 2008). The proposed mechanism by which PA restores ovulation starts with enhanced insulin sensitivity, which aids in the restoration of normal levels of steroidogenesis (Hakimi and Cameron, 2017). Research suggests that increases in sex hormone-binding globulin and decreases in free androgens, resulting from increased insulin sensitivity, have the capacity to restore the GnRH cycle, leading to spontaneous ovulation in women with PCOS (Froment and Touraine, 2006).

Very little is known about the effects of PA on reproductive health outcomes, such as infertility and menstrual irregularities, in the general population. In the context of increasing population levels of rates of overweight and obesity in young adult women, (Gomersall et al., 2014; Australian Bureau of Statistics, 2015; Brown et al., 2016) and the increasing numbers of women seeking help for fertility problems (Herbert et al., 2009), it is important to understand whether PA could help with management of reproductive health problems, with or without weight loss. The primary aim of this systematic review and meta-analysis was therefore to assess the effects of PA on selected reproductive health outcomes in young adult women, in order to develop evidence-based advice for women in terms of promoting fertility and reproductive health in young adulthood.

Methods

Protocol and registration

This systematic review was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42018094169, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018094169) and undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2010).

Eligibility criteria

Papers were selected if they were as follows:

- intervention studies such as randomized controlled trials (RCTs), quasi-experimental studies (with or without a control or comparison group) or other non-randomized clinical trials;
- included premenopausal women aged 18–46 years;
- described any type (aerobic, endurance, or resistance) of PA intervention;
- described outcome measures related to fertility; and
- published between 1 January 2000 and May 2018, in English or Spanish.

There was no restriction in terms of associated risk factors for infertility such as PCOS or overweight and obesity. Hence, women with any BMI were included.

Information sources and search terms

The following electronic databases were used to identify potentially eligible studies: PubMed, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Web of Science, SportDiscus, and Cochrane. The reference lists of eligible studies were hand searched to identify further studies.

Search terms included keywords for three domains: PA, reproductive outcomes in women (fertility), and weight gain. The search terms were adapted for each database, with keywords searched in full text and Medical Subject Headings. Results were refined by the following additional filters: 'humans' and 'female' gender and, when possible, by study design (RCTs, clinical trials, controlled clinical trials, etc.). Additional search terms for study design were used when the database did not offer the option of study design selection. A summarized search strategy is presented in Supplementary Table SI.

Study selection and data extraction

Results of the searches were exported to a citation manager (EndNote version X8.2) for removal of duplicates. Titles and abstracts of the retrieved papers were screened by one author (G.M.) and verified by another (W.B.), before retrieving full-text versions for data extraction. Each study was read in full to extract information on the following: study design, country, participant information, sample size, intervention, comparison, intervention duration, follow-up period, dropouts, number of participants included in the analysis, outcomes (both reproductive and those related to weight gain), and method used for validation of the outcome. Study authors were contacted to request missing data in one paper (Duval et al., 2015).

Risk of bias in individual studies

Study quality and reporting were assessed using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX; Smart et al., 2015). This tool includes a checklist of 12 items for 15 points. Five of the 15 possible points are related to study quality and 10 to study reporting. One point is awarded for the following study quality criteria: eligibility criteria, randomization, allocation concealment, groups similar at baseline, and blinding of assessor for at least one key outcome. For study reporting, the remaining 10 points are distributed between six items. Points are awarded if adherence was >85%; adverse effects were reported; exercise attendance was reported; intention-to-treat (ITT) analysis was performed; between-group statistical comparisons were reported for the primary outcome measure and for the secondary outcome measure; point estimates were reported; there was activity monitoring in control groups; exercise load was adjusted to keep relative intensity constant; and exercise volume and expenditure could be calculated. Higher scores reflect better study quality and reporting. The assessment of quality was performed by two researchers (G.P.M. and W.B.) and in cases of discrepancy the third author was consulted.

Synthesis of results

Papers were categorized by study design (RCTs, comparison trials, or single-arm clinical trials), and data relating to each reproductive health outcome were then extracted and summarized using narrative review, and, if possible, meta-analysis.

For meta-analysis, data were imported into Review Manager Version 5.3.5 (The Cochrane Collaboration, Oxford, UK). Separate analyses were performed for studies in which the PA intervention was

compared with a control (i.e. standard care or no treatment) condition and studies that compared PA with another intervention. When data were available, sub-analyses were performed to calculate risk ratios (RR) and mean between group differences (with 95% CIs) by outcome. Random effects models were used for meta-analysis. All the analyses were performed using Review Manager Software Version 5.3.5 (The Cochrane Collaboration, Oxford, UK).

Results

Study selection and characteristics

Details of the study selection process are shown in the PRISMA flow diagram (Fig. 1). The initial search retrieved 270 citations. Of these, 18 met all the inclusion criteria and were included in the narrative review (qualitative synthesis). Details of each study are summarized in Table I. Of the 18 selected studies, 4 were RCTs (with a 'no-intervention' or 'usual care' control group), 13 were comparison trials (11 randomized and 2 non-randomized comparison trials), and 1 was a single-arm clinical trial (Moran *et al*., 2011b). The comparison trials included four that used fertility treatment (e.g. clomiphene citrate, gonadotrophins, and/or IVF) and nine that used treatments for women with PCOS-related symptoms, such as metformin, diet, or the oral contraceptive pill (OCP), as the comparison intervention. Two of the 18 were pilot studies (Bruner *et al*., 2006; Moran *et al*., 2011b). Due to variation in study design and outcome measures, data from 12 trials were included in the meta-analyses (three RCTs and nine comparison trials).

As shown in Table I, four studies took place in Italy, four in Australia, two each in Sweden and Canada, and one each in Iran, Turkey, Slovakia, USA, The Netherlands, and Denmark. Of the comparison trials, six had two intervention arms, six had three intervention arms, (Thomson *et al*., 2008; Stener-Victorin *et al*., 2009; Palomba *et al*., 2010; Nybacka *et al*., 2013; Legro *et al*., 2015; Orio *et al*., 2016) and one had four groups (Karimzadeh and Javedani, 2010). Sample size varied from 12 participants in 1 pilot study (Bruner *et al*., 2006) to 577 in the Dutch study by Mutsaerts *et al*. (2016).

Description of participants

The age of participants in each trial ranged from 18 to 46 years, and BMI (reported in 13 trials) ranged from 18 to 45 kg/m^2. Although one trial included participants with normal BMI (Orio *et al*., 2016), all the others had 'overweight' (n = 5), 'obesity' (n = 5), or both (n = 6) as inclusion criteria. All the trials (n = 18) were restricted to women with reproductive health problems, such as infertility (with ongoing or past IVF), PCOS, or hyperandrogenism (Orio *et al*., 2016). In three trials, participants were anovulatory, and in one the participants had hyperinsulinemia and insulin resistance (Lazurova *et al*., 2004). Of the total 2035 participants, 769 received a PA intervention.

Description of interventions

In general, the PA interventions were poorly described, and important details that might allow their replication, such as type, frequency, intensity, and duration of the intervention were not always reported. Where described, in most cases the PA component was part of a multi-strategy or 'lifestyle' intervention (i.e. diet and counselling). Only six trials (two RCTs, Vigorito *et al*., 2007; Moran *et al*., 2011b) and four comparison trials (Palomba *et al*., 2008; Stener-Victorin *et al*., 2009; Nybacka *et al*., 2013; Orio *et al*., 2016) tested a PA component alone, while eight had both a dietary and PA component (three RCTs, Moran *et al*., 2011a; Sim *et al*., 2014b; Kaya *et al*., 2016; five comparison trials, Bruner *et al*., 2006; Thomson *et al*., 2008; Karimzadeh and Javedani, 2010; Duval *et al*., 2015; Mutsaerts *et al*., 2016). One of the comparison trials used exercise plus counselling sessions (Roessler *et al*., 2013) and three included pharmacotherapy interventions (e.g. conventional drugs for improving fertility such as clomiphene citrate (Palomba *et al*., 2010), weight loss drugs such as sibutramine (Lazurova *et al*., 2004), or drugs for the treatment of women with PCOS such as the OCP (Legro *et al*., 2015) combined with a dietary and PA intervention.

Only seven trials provided full details of the exercise intervention (type, frequency, intensity, duration, etc.). In most trials, the intervention included advice to increase PA levels (Lazurova *et al*., 2004; Stener-Victorin *et al*., 2009; Karimzadeh and Javedani, 2010; Sim *et al*., 2014b; Duval *et al*., 2015; Legro *et al*., 2015; Kaya *et al*., 2016). In 10 studies the intervention was monitored (Bruner *et al*., 2006; Vigorito *et al*., 2007; Palomba *et al*., 2008, 2010; Thomson *et al*., 2008; Moran *et al*., 2011b; Nybacka *et al*., 2013; Roessler *et al*., 2013; Mutsaerts *et al*., 2016; Orio *et al*., 2016), and in 1 study the PA intervention was a home-based programme (Moran *et al*., 2011a). One trial used a step counter to encourage participants to reach a target of 10 000 steps per day (Mutsaerts *et al*., 2016a).

PA intervention duration varied across the trials, from 6 (Palomba *et al*., 2010) to 32 weeks (Karimzadeh and Javedani, 2010), with 12 and 16 weeks the most common durations. Ten interventions involved aerobic exercise only (Vigorito *et al*., 2007; Palomba *et al*., 2008; Stener-Victorin *et al*., 2009; Palomba *et al*., 2010; Moran *et al*., 2011b; Roessler *et al*., 2013; Sim *et al*., 2014b; Legro *et al*., 2015; Mutsaerts *et al*., 2016; Orio *et al*., 2016), five included both aerobic and resistance training (Bruner *et al*., 2006; Thomson *et al*., 2008; Karimzadeh and Javedani, 2010; Moran *et al*., 2011a; Nybacka *et al*., 2013), and three did not specify the type of exercise intervention (Lazurova *et al*., 2004; Duval *et al*., 2015; Kaya *et al*., 2016). Eight trials reported that the exercise intensity remained constant throughout the intervention period (Bruner *et al*., 2006; Vigorito *et al*., 2007; Thomson *et al*., 2008; Palomba *et al*., 2010; Moran *et al*., 2011a; Roessler *et al*., 2013; Legro *et al*., 2015; Orio *et al*., 2016). Percentage of maximal oxygen consumption (VO2max) (Vigorito *et al*., 2007; Palomba *et al*., 2008, 2010; Orio *et al*., 2016) and percentage of maximum heart rate (Bruner *et al*., 2006; Thomson *et al*., 2008; Stener-Victorin *et al*., 2009; Moran *et al*., 2011a; Roessler *et al*., 2013) were the most commonly used measures of intensity. In half the trials (n = 9), details of exercise intensity were not provided (Lazurova *et al*., 2004; Karimzadeh and Javedani, 2010; Moran *et al*., 2011a; Nybacka *et al*., 2013; Sim *et al*., 2014b; Duval *et al*., 2015; Legro *et al*., 2015; Kaya *et al*., 2016; Mutsaerts *et al*., 2016).

Risk of bias within studies

In exercise training intervention trials, some traditional study quality criteria, such as blinding of the participant and the researcher, are difficult to implement. We therefore used a quality assessment tool designed specifically for use in exercise training studies (see above). One study author (Duval *et al*., 2015) responded to our request for

Table I Summary of study characteristics.

#	Study (citation)	Study design	Country	Population (inclusion criteria)	Baseline sample	Intervention (1) and control (2) groups	Description of PA intervention	Description of control arm	Follow-up duration
	RCTs								
1	Kaya *et al.* (2016)	RCT	Turkey	Infertile women who had at least two unsuccessful IUIs.	73	(1) education group: health-promoting lifestyle education ($n = 33$), (2) control group ($n = 40$)	Type: education on exercise, nutrition, interpersonal support, and stress management; intensity: NR; duration: 3 months	No intervention	NR
2	Moran *et al.* (2011a)	RCT, pilot study	Australia	Overweight/obese women undergoing IVF; age: 18–40 years; BMI ≥28, <45	46	(1) active intervention group ($n = 21$), (2) control group ($n = 25$)	Type: home-based progressive walking programme (20 min/session, 3 times/week during the first week to 30–45 min/session, 4 times/week + resistance training (2 days/wk 1–2 × 8–10 reps); intensity: moderate; duration: 5–9 weeks before oocyte pick-up. (52.6 ± 14.0 days in the active group and 53.5 ± 16.6 days in the CG); diet: reduced energy diet	Standard advice on appropriate diet and lifestyle factors influencing fertility + multivitamins	NR
3	Sim *et al.* (2014b)	RCT	Australia	Obese women undertaking fertility treatment; age: 18–37 years; BMI ≥30	49	(1) diet, exercise, and psychological/behavioural advice ($n = 27$), (2) standard care ($n = 22$)	Type: unsupervised increasing PA to a target of 10 000 steps over 6 weeks; intensity: light to moderate; duration: 3 months; diet: very-low-energy diet for initial 6 weeks, followed by hypocaloric diet (2500 kJ deficit)	Advised to see their general practitioner for weight loss advice	12 months
4	Vigorito *et al.* (2007)	RCT	Italy	Overweight women with PCOS	90	(1) PCOS-T (trained) group ($n = 45$), (2) PCOS-UnT (untrained) group ($n = 45$)	Type: 3 training sessions/week (30 min on a bicycle ergometer; intensity: moderate (60–70% of VO_2 max); duration: 3 months	No exercise training	NR
	Comparison trials								
#	**Study (citation)**	**Study design**	**Country**	**Population (inclusion criteria)**	**Baseline sample**	**Intervention (1) and comparison (2) groups**	**Description of PA intervention**	**Description of comparison arm (s)**	**Follow-up duration**
	Comparison with fertility treatment								
5	Duval *et al.* (2015)	Randomized, comparison trial (preliminary results)	Canada	Obese infertile women; age: 18–40 years; BMI ≥30 or ≥28 (with PCOS)	105	(1) Lifestyle intervention without fertility treatments for the first 6 months ($n = 24$), (2) standard fertility treatment only ($n = 31$)	Type: weekly group sessions (30–60 min each) teaching women to increase their PA level + individual encounters with a dietician and a kinesiologist; duration: 18 months or until the end of pregnancy	Standard fertility treatment, may also include lifestyle counselling	Maximum of 18 months or up to the end of pregnancy

Continued

Table I *Continued*

6	Karimzadeh and Javedani (2010)	Randomized, comparison trial	Yazd, Iran	Infertile women with PCOS; age: 19–35 years; BMI 25–29.9	343	(1) Lifestyle modification ($n = 75$), (2) clomiphene (CC) ($n = 90$), (3) metformin (M) ($n = 90$), (4) clomiphene + metformin (CC+M) ($n = 88$)	Type: aerobic exercise (30 min/day of climbing up steps or walking) and strength training (3–5 weeks for 20–60 min); duration: 8 months; diet: low-calorie diet, 500 calories less than daily requirements, including 50–60% carbohydrates, 25–30% fat, and 15–20% of proteins.	2/CC: at a dose of 100 mg on days 3–7; 3/M: initial dose of 500 mg, increased during the first 3 weeks until a total of 1500 mg/day; 4/CC+M: 2+3 in similar manner	NR
7	Mutsaerts *et al.* (2016)	Randomized, comparison trial	The Netherlands	Infertile women; age: 18-39 years; BMI ≥ 29	577	(1) Lifestyle intervention ($n = 290$), (2) standard fertility treatment ($n = 287$)	Type: unsupervised exercise 2–3 times/week (30 min) + 10 000 steps/day (monitored by a step counter); Intensity: moderate; duration: 6 months; diet: advice on reducing energy intake by 600 kcal/day while maintaining a minimum calorie intake of 1200 kcal/day; behavioural: motivational counselling; lifestyle intervention followed by infertility treatment	CC 50 mg/day for 5 days and gonadotropin therapy if ovulation was not induced + IVF	24 months
8	Palomba *et al.* (2010)	Randomized, comparison trial	Italy	Overweight/obese women with PCOS; age: 18–35 years; BMI 25–34	96	(1) SET + hypocaloric diet ($n = 32$), (2) observation + 1 cycle of CC ($n = 32$), (3) SET + hypocaloric diet + 1 cycle of CC ($n = 32$)	Type: SET: 3 training sessions/week on a bicycle ergometer (30 min); intensity: 60–70% VO_2 max; duration: 1.5 months; diet: hypocaloric diet: high protein composition (35% protein, 45% carbohydrate, and 20% fat), and a 1000 kcal deficit per day	2/Observation+ CC: a fixed dose of 150 mg/day for 5 days; 3/SET + Diet + CC	NR
	Other comparison trials								
9	Palomba *et al.* (2008)	Non-randomized, comparison trial	Italy	Obese women with PCOS and anovulatory fertility; age: 18–35 years; BMI of 31–35	40	(1) SET group ($n = 20$); (2) Hypocaloric hyperproteic diet (Diet group) ($n = 20$)	Type: SET: 3 training sessions/week on a bicycle ergometer (30 min); intensity: 60–70% VO_2 max; duration: 6 months	Diet group: high protein composition (35% protein, 45% carbohydrate, and 20% fat) and an 800 kcal deficit per day + multivitamin/ mineral supplement	NR
10	Lazurova *et al.* (2004)	Non-randomized, comparison trial	Slovakia	Overweight/obese women with chronic anovulation, hyperinsulinemia, and insulin resistance (with or without PCOS)	45	(1) sibutramine + diet and exercise ($n = 15$), (2) metformin only (M) ($n = 30$)	Type: unsupervised exercise; duration: 4 months; diet: low-calorie diet + oral administration of 10 mg sibutramine daily.	Metformin 500 mg twice/day	NR

Continued

Table I *Continued*

11	Nybacka *et al.* (2013)	Randomized, comparison trial	Sweden	Overweight/obese women with PCOS	57	(1) exercise ($n = 19$), (2) diet ($n = 19$), (3) diet and exercise ($n = 19$)	Type: endurance, aerobic, (walking (with or without poles), aerobics, jogging, swimming) and muscle strength training and/or weight training 2–3 times/week (45–60 min); intensity: moderate to vigorous; duration: 4 months (monitored by pedometers)	2/Diet: daily caloric intake reduced by ≥600 kcal/d, 55–60% carbohydrates, 25–30% fat (10% saturated), and 10–15% proteins; 3/Combination of diet and exercise	33 [19–56] months after termination of the intervention
12	Thomson *et al.* (2008)	Randomized, comparison trial	Australia	Overweight/obese women with PCOS; age: 18–41 years; BMI 22–55	94	(1) Diet and aerobic exercise (DA) ($n = 31$), (2) diet and combined aerobic-resistance exercise (DC) ($n = 33$), (3) diet only (DO) ($n = 30$)	1/Type: diet + aerobic (5 × 25–45 min walk/jog per week); intensity: 60–80% HR_{max}; 2/Type: combined: DA + resistance training (3 × 12, 2 times/week); intensity: vigorous (training load of 50–60% 1RM in the first 2 weeks and increased to 65–75% 1RM for the following weeks); duration: 5 months	3/High-protein diet (5000–6000 kJ/d). 30% of energy as protein, 40% as carbohydrate, and 30% as fat (8% saturated fat)	NR
13	Bruner *et al.* (2006)	Randomized, comparison trial, pilot study	Canada	Obese women with PCOS	12	(1) exercise and nutritional counselling ($n = 7$), (2) nutritional counselling only ($n = 5$)	Type: group nutrition sessions (1/week) + 3 sessions/week: aerobic exercise (walk/cycle for 30 min) + resistance training (2–3 × 10–15 reps); intensity: 70–85% predicted HR_{max}; duration: 3 months	Nutritional counselling only	NR
14	Stener-Victorin *et al.* (2009)	Randomized, comparison trial	Sweden	Women with PCOS; age: 30.43 (mean); BMI 27.3 (mean)	20	(1) physical exercise ($n = 5$), (2) low-frequency electroacupuncture ($n = 9$), (3) untreated CG ($n = 6$)	Type: unsupervised aerobic exercise at least 3 times/week (30–45 min); intensity: moderate (HR above 120/min) + one phone call for guidance on how to increase the physical exercise/week; duration: 4 months	2/Low-frequency EA: 2 Hz (14 × 30 min treatments); 3/CG: general advice on the importance to be physically active	NR
15	Roessler *et al.* (2013)	Randomized, comparison trial	Denmark	Overweight women with PCOS; age: 19–46 years; BMI 25–40	17	(1) 8 weeks of HI aerobic exercise (AE) followed by 8 weeks of group counselling (GC) ($n = 8$), (2) GC then AE (crossover) ($n = 9$)	Type: HI aerobic exercise: 3 training sessions/week (2 days of indoor cycling and 1 day of brisk walking or running). Ramp-up period in the first 2 weeks (25 min brisk walking + 30 s running intervals) followed by HI exercise sessions (10 min warm-up followed by 45 min of intermittent exercise (20 s–3 min work at HR = 80–100% and 25 s–3 min rest at HR = 45–65%); intensity: ramp up: moderate 70–75% HR_{max}, high: 80–100% HR_{max}; the intensity of the walking/running sessions increased to reach 45 min with 3–5 min of running/brisk walking intervals (HR = 80–90%) and 1 min of rest (moderate walking HR = 50–60%) for 6 weeks; duration: 4 months	Counselling group sessions for 8 weeks	NR

Continued

Table I *Continued*

16	Legro *et al.* (2015)	Randomized, comparison trial	USA	Women with PCOS; age: 18–40 years; BMI 27–42	149	(1) Lifestyle group ($n = 50$), (2) OCP group ($n = 49$), (3) combined group ($n = 50$); NOTE: the three groups received ovulation induction consisting of four consecutive cycles of CC	Type: aerobic exercise (10 min/day for the first 5 days and gradually increased over 4 months to 30–35 min/day) 5 days/week; duration: 4 months; diet: caloric restriction: at least 15% calories from protein, <30% calories from fat, and the remaining calories from CH + behavioural lessons + sibutramine 5 mg/day up to a max dose of 15 mg/day (if BMI ≥30)	2/OCP: continuous OCP 20 mcg ethinyl estradiol/1 mg norethindrone acetate every day; 3/lifestyle + 2	Pregnancies were followed by trimesters until delivery
17	Orio *et al.* (2016)	Randomized, comparison trial	Italy	Women with oligo-anovulation and/or biochemical hyperandrogenism; age: 18–40 years; BMI 18–30	150	(1) SET group ($n = 50$), (2) OCP group ($n = 50$), (3) CG ($n = 50$)	Type: SET: 3 training sessions/week on a bicycle ergometer (45 min); intensity: 60–70% VO_2 max; duration: 6 months	2/OCs: 1 cp/day for 21 days each month (drospirenone 3 mg plus ethinylestradiol (EE) 30 µg); 3/CG: 1 tablet of polyvitamin/ day	3 and 6 months post intervention
	Clinical trials, single arm								
#	**Study (citation)**	**Study design**	**Country**	**Population (inclusion criteria)**	**Baseline sample**	**Intervention arm**	**Description of PA intervention**	**Description of comparison arm**	**Follow-up duration**
18	Moran *et al.* (2011b)	Clinical trial, single arm	Australia	Overweight; women with and without PCOS	15 (7 with PCOS, 8 without PCOS)	(1) Intensified endurance exercise training programme	Type: 3 sessions/week (1 h on a treadmill alternating moderate and high intensity for 5 min × 6–8 intervals with recovery times of 1–2 min); intensity: moderate (60–70% VO_2 max, 75–85 HR_{max}); high (95–100% VO_2 max, 95–100% HR_{max}); duration: 3 months	No comparison	NR

RCT, randomized controlled trial; HI, high intensity; NR, not reported; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome; SET, structured exercise training; BMI = kg/m^2

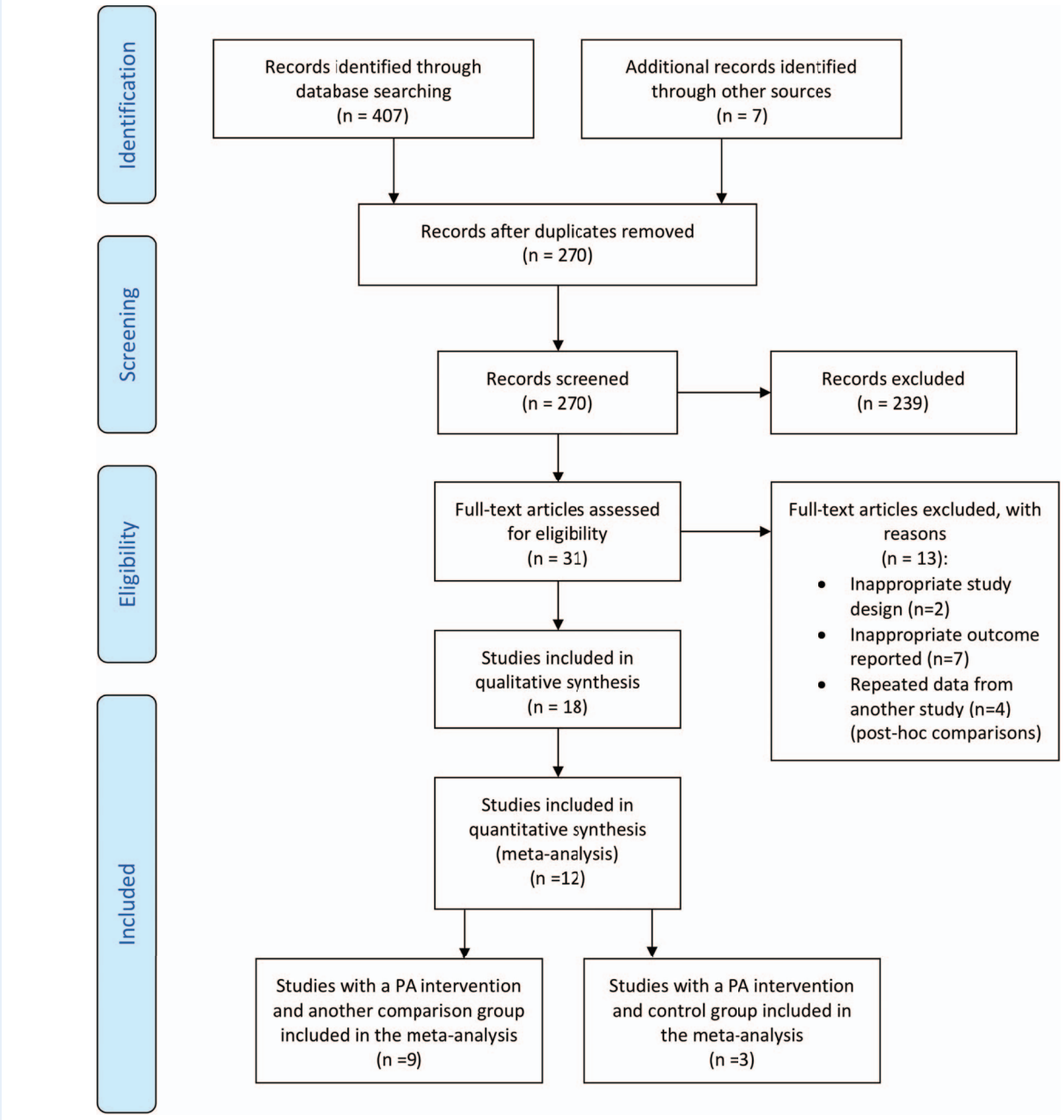


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for selecting studies for the systematic review and meta-analysis. PA, physical activity.

further information, but as no further data were available, no quality assessment could be made. Results of the assessment of quality for the randomized trials using the 15-item/points tool are shown in Supplementary Table SII. The lowest score was 6 (Karimzadeh and Javedani, 2010), and the highest was 15 (/15) (Palomba *et al*., 2010). Most trials were of moderate quality, and the median score was 10/15. All reported the eligibility criteria for participation. When assessing randomization, all trials except three specified the method of randomization used (Vigorito *et al*., 2007; Karimzadeh and Javedani, 2010; Roessler *et al*., 2013). In terms of participant allocation and similarity of the groups at baseline, all the trials scored 1 for each criterion. The TESTEX tool does not score participant and research blinding; however, it does allocate 1 point to blinding of outcome assessors. For this criterion, only 4 trials scored 1 point (Vigorito *et al*., 2007; Palomba *et al*., 2010; Sim *et al*., 2014b; Orio *et al*., 2016). Most failed to provide reports of adverse effects or session attendance. Similarly, only seven reported the exercise volume and energy expenditure (Bruner *et al*., 2006; Vigorito *et al*., 2007; Thomson *et al*., 2008; Palomba *et al*., 2010; Nybacka *et al*., 2013; Roessler *et al*., 2013; Orio *et al*., 2016). All the trials scored 1 point for statistical comparisons and point measures

of variability for the outcomes. Only four did not use ITT analysis (Bruner *et al*., 2006; Karimzadeh and Javedani, 2010; Nybacka *et al*., 2013; Roessler *et al*., 2013). One point was awarded to the study by Nybacka *et al*. (2013) for using the missing at random approach, as this is believed to be generally more accurate than older methods for handling missing data. As Vigorito *et al*. (2007) reported no missing data in their trial, the ITT approach was not applicable and 1 point was awarded for this criterion.

In addition to the TESTEX tool, we recorded the method of verification of the outcome. Most trials reported objective methods of outcome verification, such as serum hormones and ultrasound images. For the outcome 'pregnancy', five measured β-hCG in serum as a method of verification (Palomba *et al*., 2008; Karimzadeh and Javedani, 2010; Duval *et al*., 2015; Legro *et al*., 2015; Kaya *et al*., 2016), and of these, all except the trial by Duval *et al*. (2015) relied on ultrasonographic evidence of a gestational sac and/or fetal heartbeat. One trial did not measure serum hormones but verified pregnancy by ultrasound (heart beat at 7-week gestation) (Sim *et al*., 2014b). For verification of ovulation, most trials used serum hormone levels (serum progesterone) (Lazurova *et al*., 2004; Palomba *et al*., 2008, 2010; Nybacka *et al*., 2013; Legro *et al*., 2015) while others measured urinary pregnanediol-glucoronide (PDG) (Thomson *et al*., 2008; Moran *et al*., 2011b). One also included an ultrasonographic image of a dominant ovarian follicle ($\geq$12 mm) as part of the ovulation assessment (Palomba *et al*., 2010). For menstrual irregularity, menstrual cycle history was self-reported and recorded by the participants in menstrual diaries (Vigorito *et al*., 2007) or in menstrual calendars (Thomson *et al*., 2008). One trial asked participants to record menstrual bleeding on a rank analogue scale from 0 to 10 (Palomba *et al*., 2010).

Outcomes

The reproductive health outcomes from the 18 studies included in this review are shown in Table II. For meta-analyses, we present results separately for the following: trials in which the PA intervention was compared with a no treatment control (RCTs) (three studies) and trials where there was a comparison group that comprised fertility treatment or other pharmacological therapy, diet, etc. (nine trials). In order to overcome the mix of active comparison treatments, we split the second group into the following: 'fertility treatment' trials (those that used standard fertility treatment, such as clomiphene citrate, gonadotrophins, and/or IVF) and 'other comparison' trials (those that used metformin, diet, sibutramine, or OCP, which are commonly used for treating symptoms in women with PCOS). Where feasible, meta-analyses were performed separately for these three groups, and sub-analyses were performed for each specific outcome as reported below.

RCTs

Pregnancy and live births. Aggregated data from three of the four RCTs are shown in Fig. 2. The pregnancy rate was higher in women in the PA intervention groups (37/71; 52.1%) than in women who received conventional/standard treatment (16/68; 23.5%; RR 2.10, 95% CI: 1.32, 3.35). Two of these trials also reported on live births. As for pregnancies, there was a higher rate of live births in the PA interventions [19/45 (42.2%) than in the control groups, 8/42 (19.0%); RR 2.11; 95% CI: 1.02, 4.39]. As these three trials showed similar effects, heterogeneity, as indicated by I^2, was very low (Fig. 2).

Other outcomes: menstrual irregularity and conception. As only one of the trials with a control group reported on menstrual regularity (Vigorito *et al*., 2007) and similarly, only one reported on conception rates (Sim *et al*., 2014b), meta-analysis for these outcomes could not be performed. However, as shown in Table II, Sim *et al*. (2014b) reported higher rates of natural conception in the PA intervention group (3/27; 11.1%) than in the control group (0/22; 0%). In the trial by Vigorito *et al*. (2007), 60% (27/45) of women in the trained group showed normal menstrual cycles after the intervention. Without results from the untrained group (control), we cannot draw conclusions from this trial.

Comparison trials

As two of the comparison studies used both a 'fertility treatment' and an 'other comparison' for PCOS treatment (Karimzadeh and Javedani, 2010; Palomba *et al*., 2010), the results of those studies are included in both the following analysis groups.

Comparison with fertility treatment

Pregnancy. Analysis of pooled data from four studies that compared PA with fertility treatment (i.e. standard fertility treatment: clomiphene citrate, gonadotrophins, and/or IVF) showed a higher rate of clinical pregnancy in the PA intervention groups (218/486; 57.8%) than in the comparison groups (214/517; 41.4%), but the difference was not statistically significant (RR 1.46, 95% CI: 0.87, 2.45) (one study had two different comparison groups; see Fig. 3). Results from one of these trials, which compared weekly group sessions with a kinesiologist and a dietitian with standard fertility treatment, showed that the spontaneous pregnancy rate was markedly higher in the intervention group (50%) than in the comparison group (12.9%) (Duval *et al*., 2015; Table II).

Live births. Two of the fertility treatment comparison trials that reported pregnancy also reported on live births. Pooled data did not favour the PA interventions over standard fertility treatment (RR 1.09; 95% CI: 0.56, 2.12) (Fig. 3).

Improved menstrual irregularity. Two fertility treatment comparison trials reported on menstrual regularity (Karimzadeh and Javedani, 2010; Palomba *et al*., 2010). In both trials, the PA intervention improved menstrual patterns. Pooled data from these trials showed slightly, but not significantly, higher rates of improved menstrual regularity in the PA intervention groups (111/182; 61%) than in the comparison groups (118/210; 56.2%); RR 1.11; 95% CI (0.83, 1.49) (Fig. 3; there are three estimates from the two studies as one had two different comparison groups).

Conception. Only one fertility treatment trial reported on conception rates (Mutsaerts *et al*., 2016). In this study by Mutsaerts *et al*. (2016), the largest trial included in this review, women in the intervention arm (diet + exercise + behavioural counselling) achieved higher natural conception rates (73/280; 26.1%) than those in the comparison arm (46/284; 16.2%).

Other comparison trials

Meta-analyses of data from the studies that used other comparisons for treating PCOS symptoms (metformin (Lazurova *et al*., 2004; Karimzadeh and Javedani, 2010), diet (Palomba *et al*., 2008, 2010; Thomson *et al*., 2008; Nybacka *et al*., 2013) or the OCP (Legro *et al*., 2015), are shown in Fig. 4.

Table II Reproductive health outcomes.

	RCTs							
#	**Study (citation)**	**Intervention arm**	**Pregnancies per participant**	**Improved ovulation per anovulatory participant**	**Improved menstrual regularity/irregular menses per participant**	**Live births per participant**	**Conception rate**	**Other**
1	Kaya *et al.* (2016)	(1) Education group (EG): health-promoting lifestyle education ($n = 33$), (2) control group (CG) ($n = 40$)	EG = 46.1% (12/26), CG = 19.2% (5/26), $P = 0.02$					
2	Moran *et al.* (2011a)	(1) Intervention group (IG) ($n = 21$), (2) CG ($n = 25$)	IG = 66.7% (12/18), CG = 40% (8/20), $P = 0.119$			IG = 38.9% (7/18), CG = 25% (5/20)		
3	Sim *et al.* (2014)	(1) IG: diet, exercise, and psychological/behavioural advice ($n = 27$), (2) CG: standard care (SC) ($n = 22$)	Clinical pregnancy: IG = 48.1% (13/27), CG = 13.6% (3/22), $P < 0.05$; assisted pregnancy: IG = 37% (10/27), CG = 13.6% (3/22), $P = 0.06$			IG = 44.4% (12/27), CG = 13.6% (3/22)	IG = 11.1% (3/27), CG = 0% (0/22)	Miscarriage rate: IG = 29.4% (8/27), CG = 25% (6/22)
4	Vigorito *et al.* (2007)	(1) PCOS-T (trained) group ($n = 45$), (2) PCOS-UnT (untrained) group			PCOS-T = 60% (27/45) showed normal menstrual cycles, PCOS-UnT = no results reported			
	Comparison trials							
#	**Study (citation)**	**Intervention arm**	**Pregnancies per participant**	**Improved ovulation per anovulatory participant**	**Improved menstrual irregularity/irregular menses per participant**	**Live births per participant**	**Conception rate**	**Other**
	Comparison with fertility treatment							
5	Duval *et al.* (2015)	(1) Lifestyle intervention without fertility treatments for the first 6 months (IG), (2) control group (CG): standard fertility treatment only	Pregnancy rate: IG = 79.2% (19/24), CG = 41.9% (13/31), $P = 0.003$; spontaneous pregnancy rate: IG = 50.0% (12/24), CG = 12.9% (4/31), $P = 0.003$			IG = 62.5% (15/24), CG = 38.7% (12/31), $P = 0.08$		

Continued

Table II *Continued*

6	Karimzadeh and. Javedani (2010)	(1) Lifestyle modification (LM) ($n = 75$), (2) clomiphene (CC) ($n = 90$), (3) metformin (M) ($n = 90$), (4) clomiphene + metformin (CC+M) ($n = 88$)	LM = 20% (15/75), CC = 12.2% (11/90), M = 14.4% (13/90), CC+M = 14.8% (13/88), P=0.56		LM = 66.6% (50/75), CC = 66.6% (60/90), M = 55.5% (50/90), CC+M = 62.5% (55/88), $P = 0.38$			
7	Mutsaerts *et al.* (2016)	(1) Lifestyle intervention (IG) ($n = 290$), (2) control group (CG) ($n = 287$)	Ongoing pregnancy: IG = 53.6% (150/280), CG = 58.8% (167/284); clinical pregnancy: IG = 62.5% (175/280), CG = 65.5% (186/284)			Vaginal birth of a singleton: IG = 27.1% (76/280), CG = 35.2% (100/284); live birth: IG = 43.9% (123/280), CG = 53.9% (153/284)	Natural conception: IG = 26.1% (73/280), CG = 16.2% (46/284)	
8	Palomba *et al.* (2010)	(1) Group A: structured exercise training (SET) + hypocaloric diet ($n = 32$), (2) Group B: observation + 1 cycle of CC ($n = 32$), (3) Group C: SET + hypocaloric diet + 1 cycle of CC ($n = 32$)	Group A = 0% (0/32), Group B = 0% (0/32), Group C = 3.13% (1/32)	Group A = 12.5% (4/32), Group B = 9.4% (3/32), Group C = 37.5% (12/32)	Menstrual bleeding: Group A = 12.5% (4/32), Group B = 9.4% (3/32), Group C = 34.4% (11/32)			
	Other comparison trials							
9	Palomba *et al.* (2008)	(1) Structured exercise training (SET) group ($n = 20$), (2) hypocaloric hyperproteic diet (diet group) ($n = 20$)	Cumulative pregnancy rate: SET = 35% (7/20), Diet = 10% (2/20) $P = 0.058$; pregnancy rate (# pregnancies/# observed cycles): SET = 6.2% (7/113), Diet = 1.7% (2/119), $P = 0.075$	Cumulative ovulation rate: SET = 65% (13/20), Diet = 25% (5/20), $P = 0.011$; ovulation rate (# ovulatory cycles/# observed cycles): SET = 24.8% (28/113), Diet = 15.1% (18/119), $P = 0.032$	Menses frequency: (# observed menses/# expected cycles): SET = 26.2% (28/107), Diet = 15.3% (18/118), $P = 0.043$			Abortion rate (# abortions/# pregnancies): SET = 14.2% (1/7), Diet = 0% (0/2), $P = 0.075$

Continued

Table II *Continued*

10	Lazurova *et al.* (2004)	(1) Sibutramine + diet and exercise (S+D+E) ($n = 15$), (2) metformin only (M) ($n = 30$)	In women with improved menstrual cycle: S+D+E = 12.5% (1/8) M = 28.6% (6/21), total sample: S+D+E = 6.7% (1/15), M = 20% (6/30)		S+D+E = 55% (8/15), M = 70% (21/30)		
11	Nybacka *et al.* (2013)	(1) Exercise ($n = 19$), (2) diet ($n = 19$), (3) diet and exercise ($n = 19$)		Exercise = 35% (6/17), diet = 36% (5/14), diet + exercise = 33% (4/12)	Amenorrhea shifted to oligomenorrhea/regular menstruation		Significant overall change in AMH ($P < 0.05$), with a different response in the diet and the exercise group ($P < 0.01$)
12	Thomson *et al.* (2008)*	(1) Diet and aerobic exercise (DA) ($n = 31$), (2) diet and combined aerobic-resistance exercise (DC) ($n = 33$), (3) diet only (DO) ($n = 30$)	DA = 3.2% (1/31), DC = 3% (1/33), DO = 3.3% (1/30)	Of the 53 women with menstrual irregularities at baseline*, 49.1% reported improvements. Ovulation: DA = 50.0% (3/6), DC = 42.9% (3/7), DO = 50% (6/12)	Menstrual cyclicity: DA = 42.9% (9/21), DC = 44.4% (8/18), DO = 21.4% (3/14)		
13	Bruner *et al.* (2006)	(1) Exercise and nutritional counselling (EN) ($n = 7$), (2) nutritional counselling only (N) ($n = 5$)	For both groups: 8.33 % (1/12)	For both groups: 8.33 % (1/12)		For both groups: 8.33 % (1/12)	There were no significant differences in ovarian follicle population (# of follicles in each ovary) in either ovary between the groups.

Continued

Table II *Continued*

14	Stener-Victorin *et al.* (2009)	(1) Physical exercise (PE) ($n = 5$), (2) low-frequency electroacupuncture ($n = 9$), (3) untreated CG ($n = 6$)			Menstrual bleeding pattern: low-frequency EA = 71.4% (5/7 OM/AM) reported three to four menstruations during the intervention; PE = no change in menstrual patterns; CG = no change in menstrual bleeding pattern			
15	Roessler *et al.* (2013)	(1) 8 weeks of HI aerobic exercise (AE) followed by 8 weeks of group counselling (GC) ($n = 8$), (2) GC then AE (crossover) ($n = 9$)			Regular menses: 14.3% (2/14) (in both groups)			Change from a polycystic to normal configuration of the ovaries: 21.4% (3/14) for the whole group; ovarian volume decreased from 12.7 to 12.2 mL for the whole group. Volume increased immediately after PA (AE:GC 11.5 to 13.4 mL and GC:AE 11.4 to 12.8 mL)
16	Legro *et al.* (2015)	(1) Lifestyle group ($n = 50$), (2) oral contraceptive group (OCP) ($n = 49$), (3) combined group $n = 50$; NOTE: the three groups received four consecutive cycles of CC	Clinical pregnancy: lifestyle = 26% (13/50), OCP = 14.3% (7/49), combined = 26% (13/50)	Lifestyle = 60.3% (82/136), OCP = 46.1% (71/154), combined = 67.1% (94/140) (total # of ovulations/total treatment cycles)		Lifestyle = 26%(13/50), OCP = 10.2% (5/49), combined = 24% (12/50)	Lifestyle = 32% (16/50), OCP = 16.3% (8/49), combined = 28% (14/50)	Fecundity per ovulated patient: lifestyle = 36.1% (13/36), OCP = 13.9% (5/36), combined = 30.8% (12/39)

Continued

Table II *Continued*

17	Orio *et al.* (2016)	(1) Structured exercise training programme (SETP) ($n = 50$), (2) oral contraceptives (OC) group ($n = 50$), (3) CG ($n = 50$)			The frequency of menses significantly improved in both the SETP ($P < 0.01$) and OCs groups ($P < 0.01$) after treatment. However, it was significantly higher in the OC group than the SETP group at 6m follow-up ($P < 0.01$)			
	Clinical trials, single arm							
#	**Study (citation)**	**Intervention arm**	**Pregnancies per participant**	**Improved ovulation per anovulatory participant**	**Improved menstrual irregularity/irregular menses per participant**	**Live births per participant**	**Conception rate**	**Other**
18	Moran *et al.* (2011b)	(1) Intensified endurance exercise training programme		6.7% (1/15)	6.7% (1/15)			Significant interaction between AMH changes with exercise and PCOS status ($P = 0.007$). PCOS had no change in AMH ($+1.4 \pm 5.2$ pmol/l, $P = 0.48$) while women with PCOS had a decrease in AMH (-13.2 ± 11.7 pmol/l, $P = 0.025$)

AMH, anti-Müllerian hormone AM, amenorrhea

*Data on reproductive functions from 59 women due to inconclusive results from PDG analysis and menses calendars for the remaining subjects.

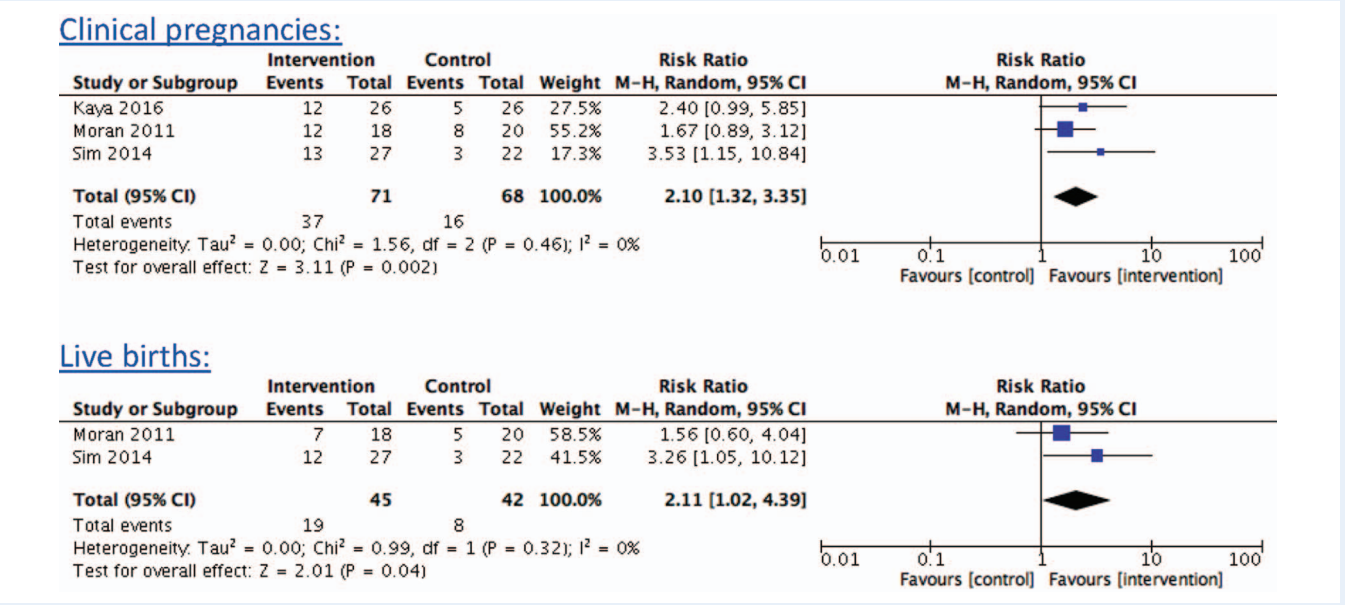


Figure 2 Forest plots of PA randomized controlled trials for the outcomes of clinical pregnancies and live births.

Pregnancy. Data from six of these studies (eight comparisons) showed a higher pregnancy rate for women in the PA intervention groups (52/306; 17%) than for those in the other comparison groups (37/330; 11.2%); RR 1.59, 95% CI (1.06, 2.38) (Fig. 4).

Live births. Pooled data from a three-arm study that compared lifestyle, OCP, and lifestyle + OCP combined showed a higher rate of live births in the lifestyle groups (25/100; 25%) than in the OCP only group (10/98; 10.2%; RR 2.45; 95% CI: 1.24, 4.83) (Legro *et al.*, 2015). In this study, the continuous OCP was used as part of preconception infertility treatment in a population of women with PCOS, in whom the OCP is commonly used in pretreatment for treating symptoms related to hyperandrogenism.

Ovulation improvement. Six trials reported on improved ovulation in anovulatory participants. One could not be included in the meta-analysis because the numbers of cases (of improvement) in each group were not reported (Bruner *et al.*, 2006). Another was not included because it reported ovulation rates derived by dividing the total number of ovulations by the total number of treatment cycles (Legro *et al.*, 2015). In this three-arm trial all the patients were treated with four consecutive cycles of clomiphene citrate regardless of group allocation. The group whose clomiphene citrate treatment was preceded by a combined lifestyle + OCP intervention (diet + exercise + behavioural component + OCP) had a higher ovulation rate (94/140; 67.1%) than the OCP only group (71/154; 46.1%). Of the remaining trials in this group, one reported minor differences in ovulation rates with diet (5/14, 36%) and exercise (6/17, 35%) interventions (Nybacka *et al.*, 2013), and a non-randomized trial showed that the cumulative ovulation rate in the structured exercise training group was higher (65%; 13/20) than in the diet group (25%; 5/20) (Palomba *et al.*, 2008). Another three-arm trial reported a 50% improvement in ovulation rates in the diet only (6/12) and diet and aerobic exercise groups (3/6) and a 43% (3/7) improvement in the diet and combined aerobic and resistance exercise group (Thomson *et al.*, 2008). However, from a baseline sample of 94, data on reproductive function were only from 59 women, due to inconclusive results from the urinary PDG analysis.

Results of the meta-analysis of data from six comparisons reported in four studies found a higher rate of ovulation improvement in the PA intervention (43/99; 43.4%) than in the other comparison groups (30/102; 25%); RR 1.42, 95% CI (0.90, 2.24), but the difference was not statistically significant (Fig. 4).

Improved menstrual irregularity. Seven trials reported on menstrual regularity. In four of these, the PA intervention improved menstrual patterns (Palomba *et al.*, 2008; Thomson *et al.*, 2008; Nybacka *et al.*, 2013; Orio *et al.*, 2016). Of the remainder, one trial found improvement in both groups (Roessler *et al.*, 2013), one reported no change in either group (Stener-Victorin *et al.*, 2009), and in one, the comparison group (metformin) performed better than the intervention (Lazurova *et al.*, 2004). The biggest effect was in a three-arm trial; the two combined exercise and diet groups showed higher rates of improvement (diet + aerobic = 42.9%; diet + combined aerobic and resistance training = 44.4%) than the diet only group (21.4%) (Thomson *et al.*, 2008). All except one trial reported the number of women experiencing menstrual improvement. In it, the researchers based their results on the number of cycles (Palomba *et al.*, 2008).

Pooled data from the trials that used 'other comparisons' (five studies, six estimates) show that the rate of improved menstrual regularity was higher in the intervention groups (114/268; 42.5%) than in the comparison groups (99/298; 33.2%), but the difference was not quite statistically significant (RR 1.37; 95% CI: 0.97, 1.93) (Fig. 4).

Conception. Only two trials reported on conception rates (Bruner *et al.*, 2006; Legro *et al.*, 2015). The study by Bruner *et al.* (2006) did not report estimates for both groups. In the study by Legro *et al.* (2015), women in the lifestyle intervention arm had a higher conception rate (16/50; 32%) than those in the other comparison arms (8/49; 16.3% and 14/50; 28%), which included a group receiving the OCP and a group that received combined lifestyle plus OCP treatment,

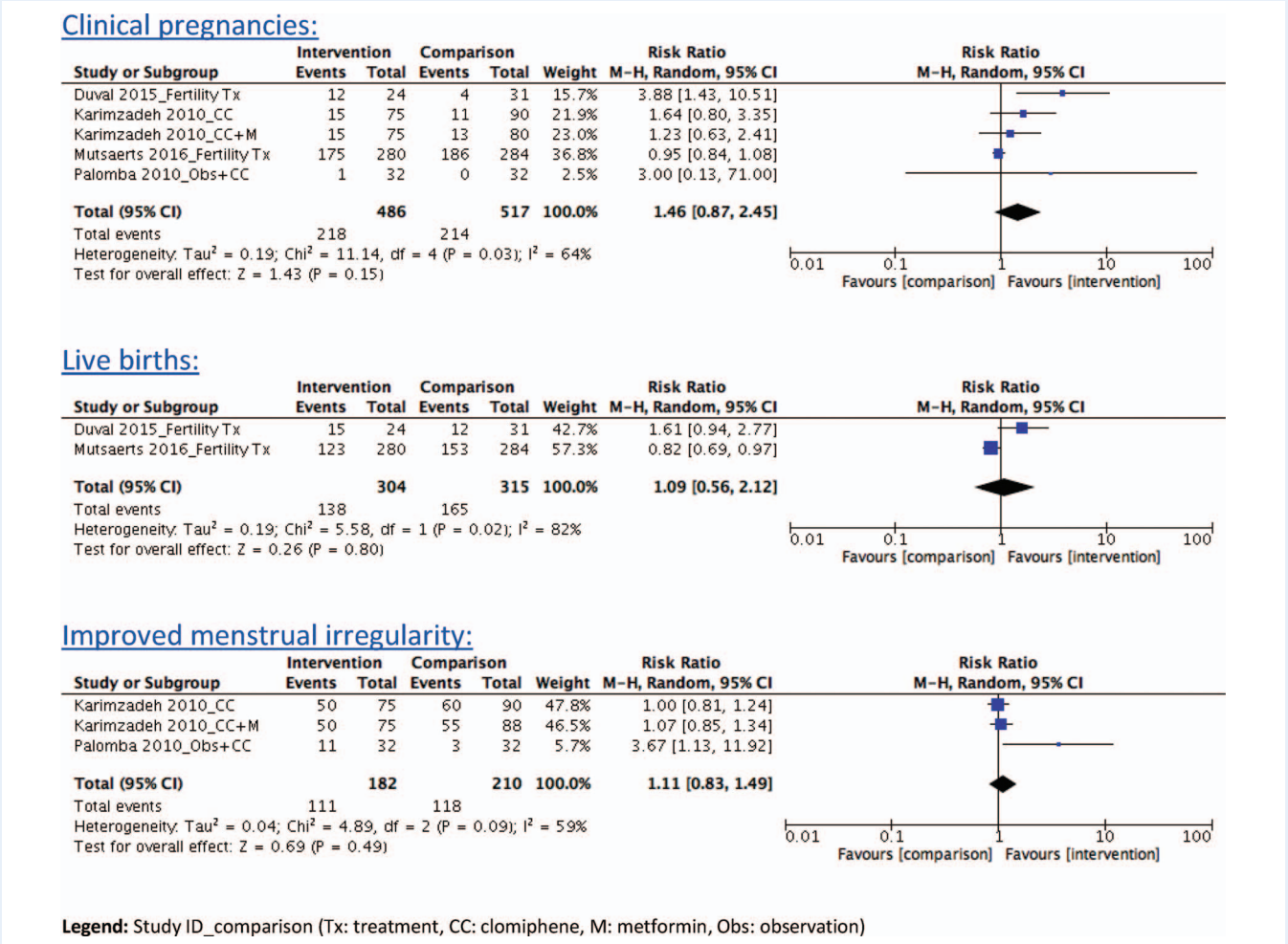


Figure 3 Forest plots of comparison trials of PA and fertility treatments for the outcomes of clinical pregnancies, live births, and improved menstrual irregularity.

respectively. All three groups in this study received ovulation inductors (i.e. clomiphene citrate). Therefore, it is assumed that the reported rates do not reflect natural conception.

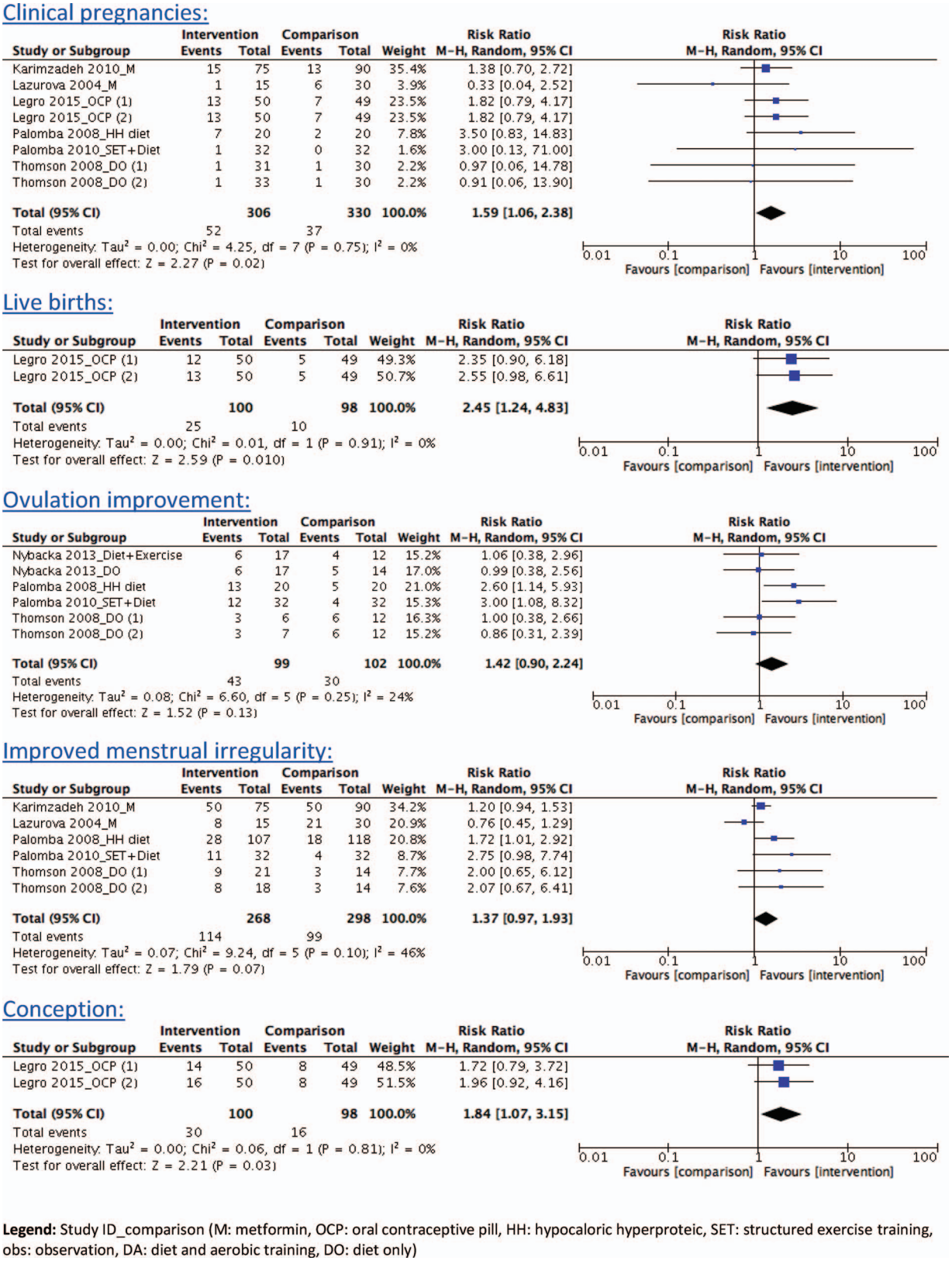
Pooled data (one study, two estimates) demonstrated that PA as part of a lifestyle intervention, either with or without the OCP, showed greater improvement in conception rate (30/100; 30%) than the OCP only comparison group (16/98; 16.3%); RR 1.8; 95% CI: 1.07, 3.15 (Fig. 4).

Weight and other body composition outcomes. Body composition measures, including weight (change), BMI, fat mass, or waist circumference, were reported in all except one trial (Kaya *et al.*, 2016), as most studies had overweight ($n = 5$), obesity ($n = 5$), or a combination of both ($n = 6$) as an inclusion criterion. Only one study included women with normal BMI (Orio *et al.*, 2016). Body composition outcomes from these 17 studies are shown in Supplementary Table SIII.

Since we were interested in the potential confounding or mediating effects of weight change in the PA intervention studies, results from the 10 studies that reported on weight change are shown in Table III. Mean weight reductions ranged from −0.2 to −10.1 kg in the PA intervention groups and from −0.2 to −10.5 kg in the comparison groups.

Two of the RCTs reported on mean weight reduction. The one that showed larger effects on clinical pregnancies and live births (Sim *et al.*, 2014) reported significantly greater mean weight loss in the intervention (6.6 kg) than in the control group (1.6 kg; $P < 0.001$). In the second, which did not show significant benefits in birth-related outcomes (Moran *et al.*, 2011a), there was also a significant difference in weight loss in the intervention (−3.8 kg) and control (−0.5 kg) groups, but the magnitude of the intervention weight loss was smaller than in the study by Sim *et al.* (2014).

In contrast, in the first group of comparison trials, (those that compared lifestyle with fertility treatments) the RRs for clinical pregnancies and live births were highest in the study by Duval *et al.* (2015), which reported only modest weight loss in both the intervention and comparison groups (Table III). In the third group ('other comparison' trials), the positive RRs for ovulation improvement in the study by Palomba *et al.* (2008) reported marked weight loss in both the intervention (−5.6 kg) and comparison groups (−10.5 kg). In light of these somewhat mixed results, the small number of RCTs, and the mixed designs of the comparative studies, it is not possible to say whether the positive effects on reproductive health



Legend: Study ID_comparison (M: metformin, OCP: oral contraceptive pill, HH: hypocaloric hyperproteic, SET: structured exercise training, obs: observation, DA: diet and aerobic training, DO: diet only)

Figure 4 Forest plots of comparison trials of PA and other interventions for the outcomes of clinical pregnancies, live births, ovulation improvement, improved menstrual irregularity, and conception.

Table III Changes in body weight: weight reduction outcomes for women in the intervention and comparison groups.

	Intervention				Comparison				
Study	**Description**	**Total (n)**	**Mean change (kg)**	**SD**	**Description**	**Total (*n*)**	**Mean change**	**SD**	**P (for group difference)**
RCTs									
Moran *et al.* (2011a)	Diet and aerobic and resistance training exercise	18	−3.8	3.0	Standard advice on diet	20	−0.5	1.2	<0.001
Sim *et al.* (2014)	Diet and exercise	26	−6.6	4.6	Standard care	17	−1.6	3.6	<0.001
Comparison trials									
Comparison with fertility treatment									
Duval *et al.* (2015)	Lifestyle intervention (diet and exercise)	28	−2.5	1.34*	Standard fertility treatment	31	−1.6	0.83*	0.05
Mutsaerts *et al.* (2016)	Lifestyle intervention (diet and exercise)	236	−4.4	5.8	Standard fertility treatment	128	−1.1	4.3	<0.001
Palomba *et al.* (2010)	Aerobic exercise + hypocaloric diet	32	−4.21	1.51*	Clomiphene citrate (CC)	32	−0.69	1.67*	<0.05
Palomba *et al.* (2010)	Aerobic exercise + hypocaloric diet	32	−4.21	1.51*	Aerobic exercise + hypocaloric diet + CC	32	−4.42	1.63*	ns
Other comparison trials									
Palomba *et al.* (2008)	Aerobic exercise (women who ovulated)	13	−5.6	1.6	Diet	5	−10.5	4.1	<0.05
Palomba *et al.* (2008)	Aerobic exercise (women who did not ovulate)	7	−2.0	0.2	Diet	15	−2.3	3.1	ns
Thomson *et al.* (2008)	Aerobic exercise + diet	18	−10.1	5.6	Diet	14	−8.6	5.3	ns
Thomson *et al.* (2008)	Aerobic + resistance training exercise + diet	20	−8.6	5.2	Diet	14	−8.6	5.3	ns
Bruner *et al.* (2006)	Aerobic exercise and nutritional counselling	7	−0.8	3.80*	Nutritional counselling only	5	−3.1	3.53*	ns
Stener-Victorin *et al.* (2009)	Aerobic exercise	29	−0.2	1.2	Standard care	15	−0.4	0.8	ns
Stener-Victorin *et al.* (2009)	Aerobic exercise	29	−0.2	1.2	Acupuncture	28	−0.2	0.8	ns
Legro *et al.* (2015)	Lifestyle intervention (diet and exercise)	50	−6.2	0.45* ($P < 0.001$)	OCP only	49	−1.1	0.42*	0.01
Legro *et al.* (2015)	Lifestyle intervention (diet and aerobic exercise) + OCP	50	−6.1	0.45* ($P < 0.001$)	OCP only	49	−1.1	0.42*	0.01

ns, no significant; ***SE**

outcomes in the PA intervention groups were attributable to weight loss.

Discussion

Summary of evidence

The overall aim of this systematic review was to investigate the effects of PA on indicators of reproductive health in young adult women. Following a systematic search, we identified only 18 PA intervention trials. The 18 trials included a mix of 4 types of study design (4 RCTs, 11 randomized comparison trials, 2 non-randomized comparison trials, and 1 single-arm clinical trial), with a range of reproductive health outcomes. This made it difficult to assess the independent effects of PA on most outcomes.

Data from the RCTs found emerging evidence of a beneficial effect of PA on indicators of fertility, such as pregnancy rates and live births. Clinical pregnancy rates were more than twice as high following PA intervention. However, these results reflect data from only three studies. Using data from other randomized comparison trials, meta-analysis showed that the effects of PA were not significantly different from those associated with a range of standard fertility treatments, which include ovulation inductors such as clomiphene citrate, gonadotrophin therapy, and/or IVF. Finally, meta-analysis of data from trials that used 'other treatment' comparisons (including metformin, hypocaloric diets, hyperproteic diets, and the OCP) showed a higher clinical pregnancy rate in the PA interventions.

Findings

Throughout this review, the complexities of the different study designs, and the wide variation in the nature and timing of the intervention and comparison strategies, made it difficult to disentangle the effects of PA from those of other intervention strategies such as diet or concurrent pharmaceutical treatments.

In the RCTs the effects were easier to assess, with positive outcomes for pregnancies and live births, but there were only three studies in this group. Also, in the only RCT that reported on conception, the PA intervention, given in conjunction with diet and behavioural advice, showed higher conception rates than standard care (Sim *et al*., 2014b).

The RCTs used a mixed approach of diet and exercise and in one study the exercise component included both aerobic and resistance training (Moran *et al*., 2011a). Only two of the studies in the meta-analysis reported on weight change. As both studies reported significantly greater weight loss in the intervention groups, it is not possible to attribute the positive effects on pregnancy rates to PA, weight loss, or a combination of both.

Results from the trials that compared PA with fertility treatments (e.g. clomiphene citrate, gonadotrophins, and/or IVF) showed that overall, there was no difference between the intervention and fertility treatment groups for the outcomes clinical pregnancies, live births, and improved menstrual irregularity. This may indicate that clinicians could try PA interventions as a first line intervention for women experiencing fertility problems.

Most common fertility treatments, with the exception of IVF, involve the use of ovulation inductors (e.g. clomiphene, which stimulates the pituitary gland to secrete gonadotrophins) or external provision of gonadotrophins (e.g. FSH and LH). Research with women with PCOS has shown that exercise acts in a similar way. It has the potential to restore the GnRH cycle, leading to spontaneous ovulation (Froment and Touraine, 2006). Additionally, there is systematic review evidence that exercise, with or without diet, can lead to resumption of ovulation in overweight/obese women with PCOS (Harrison *et al*., 2010; Hakimi and Cameron, 2017) by resetting the hypothalamic–pituitary–gonadal axis by exercise (Hakimi and Cameron, 2017).

In the subgroup of trials that used 'other comparisons', differing designs and the inclusion of 'exercise' as part of a 'lifestyle' intervention made the interpretation of the outcomes difficult. In terms of the intervention groups, only four trials had a PA only intervention (Palomba *et al*., 2008; Stener-Victorin *et al*., 2009; Nybacka *et al*., 2013; Orio *et al*., 2016) and in the rest of the trials, the PA component was given in combination with diet, sibutramine, or nutritional counselling.

Similarly, the comparison groups had a mix of interventions. Multiple comparisons from the same study were observed in most trials, and some reported results from two different comparison arms. The comparison arm interventions ranged from weight loss drugs (e.g. sibutramine), electroacupuncture, and diet, to other drugs that are commonly used to treat PCOS-related symptoms, such as metformin or the OCP. It is therefore not surprising that in most cases the rates of several reproductive health outcomes were higher in the PA interventions than in the comparison arms.

These results should be interpreted with caution, as estimates for live births and conception rates came from a single study that used the OCP in the comparison group (Legro *et al*., 2015). However, women in one of the active intervention groups, which comprised a lifestyle (diet, exercise, and behavioural) intervention also received the OCP, which is often used for reduction of androgenic symptoms in women with PCOS.

In terms of weight reduction, these trials also showed mixed results. The studies that showed improvements in the outcomes were not necessarily those that reported greater weight loss, suggesting a beneficial effect of PA even in the absence of significant weight loss. This is in line with a recent systematic review and meta-analysis, which found that studies with the highest pregnancy and live births rates were not necessarily those with highest weight loss. Similar natural conception rates were observed in the interventions and comparisons regardless of the amount of weight loss (Best *et al*., 2017).

Previous research has shown that higher BMI and increased weight are associated with primary infertility (Rooney and Domar, 2014; Dağ and Dilbaz, 2015). Hence, it is not surprising that most of the PA intervention trials reviewed in this paper focused on overweight and obese women. Several previous trials have shown that weight loss in obese and overweight women is an effective approach for improving fertility and pregnancy outcomes (Khaskheli *et al*., 2013; Kort *et al*., 2014; Dağ and Dilbaz, 2015). Similarly, a recent systematic review has reported that weight loss from diet and exercise is associated with higher chances of pregnancy, improved ovulation, and improved menstrual irregularity (Best *et al*., 2017).

However, while there seems to be a clear role for weight loss on improving reproductive outcomes, there is systematic review evidence that PA may be effective for restoring fertility, even in the absence of significant weight loss, in women with PCOS (Harrison *et al*., 2010). There is also evidence to suggest that PA improves ovarian reserve markers, regardless of weight (Surekha *et al*., 2014).

It is, however, possible that weight loss is a mediator in any relationship between PA and reproductive health outcomes, but, it is difficult to disentangle the benefits of PA from those of weight reduction. It is notable that trials in women with ovulatory disorders tend to give little information about the exercise intervention and rather focus on weight reduction even though it is not clear if weight loss is actually required (Harrison *et al*., 2010). At this stage it is impossible to determine whether the reproductive health outcomes were improved by weight loss, exercise, or a combination of both. More PA-based intervention studies that focus on normal weight women (or women with stable BMI) are required in order to truly assess the independent effects of PA on reproductive health outcomes.

Strengths and limitations

This review adds to the body of literature on the effects of PA on the reproductive health of young women. To our knowledge, only one previous review has focused on this issue, and it was restricted to trials of women with PCOS only (Harrison *et al*., 2010). We have added to the scope of that systematic review by including women with a variety of health conditions, including overweight, obesity, infertility, and PCOS. Wider inclusion criteria meant that we were able to find 18 trials, in comparison to the 8 in the review by Harrison *et al*. (2010). Another strength is that we categorized the studies by design and conducted separate meta-analyses for each design group. We also used a tool for the assessment of study quality specifically designed for exercise intervention trials, overcoming the limitations of the traditional tools to assess quality in these types of studies.

The review is, however, limited by the fact that few trials had true control groups (standard care or no treatment), and the different study designs and interventions made it difficult to evaluate the true effects of PA. An important confounder was contraception, depending on the type and dose this may have impacted menstrual regularity, ovulation, and pregnancies.

Moreover, as there was a range of types of PA (e.g. aerobic training alone or in conjunction with strength training), it is difficult to say whether any particular type of exercise is superior for improving reproductive health outcomes. Few trials reported on exercise volume or overall energy expenditure, and only seven adequately reported all exercise characteristics (intensity, frequency, mode, duration of session, and duration of intervention). There was, however, some indication of improvement in outcomes, even in trials with short intervention duration (e.g. <16 weeks). Information on attendance and adherence with intervention protocols was also poorly reported, making group comparisons difficult. The quality of the studies included in this review was moderate, with most of the studies scoring an average of 10 out of 15. Only two studies were of high quality (14 and 15/15) when assessed against the TESTEX criteria.

Other limitations included different types of reporting biases, with potential for delayed publication of the research findings (or publication of partial results only) and outcome reporting bias (when researchers may have selectively reported outcome variables with more 'positive' results, while the less positive findings remained unpublished).

Research recommendations

Well-designed but pragmatic intervention studies are needed to assess the efficacy of PA interventions in RCTs. In order to elucidate the optimal 'dose' or prescription of PA, studies with different types of exercise, of differing intensity and duration, will inform the development of clinical guidelines relating to the use of exercise as treatment for a range of reproductive health problems. Studies with longer follow-up, and with careful consideration of the potential mediating effects of weight loss, will help to unravel the effects of PA from those of weight change.

Conclusion

The findings of this review indicate that PA (alone or in combination with diet) may have beneficial effects on some reproductive health outcomes in young adult women. When interventions that had a PA component were compared with non-therapy controls and with a range of other interventions used for treating PCOS-related symptoms (e.g. metformin, diet, and OCP), the meta-analysis showed improvements in rates of clinical pregnancy and live births. Moreover, when PA interventions were compared with fertility treatments (e.g. clomiphene, gonadotrophins, and/or IVF), meta-analyses showed no significant differences for a range of outcomes. While the type, intensity, frequency, and duration of optimal PA intervention, and the role of PA independent of weight loss, remain unclear, these preliminary findings suggest that PA may be an affordable and feasible alternative or complementary therapy to fertility treatments.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

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Authors' roles

G.P.M. and W.J.B. were responsible for defining the research question and the design of the review. G.P.M. was involved in design and conduct of the search strategy, data extraction, quality assessment, analysis, drafting of the manuscript, and critical discussion. G.P.M. and W.J.B. assessed the eligibility of studies for inclusion. W.J.B. was involved in the design and conduct of the review, supervised and checked data extraction and quality assessment, and conducted several iterations of manuscript revision and critical discussion. G.I.M. checked data extraction, supervised the statistical analysis, and contributed to manuscript revision. All authors contributed to manuscript preparation and revision and have approved the final version.

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Conflict of interest

The authors declare they have no conflicts of interest relevant to the content of this review.

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